Review Series: Aspects of Interstitial lung disease: Connective tissue disease-associated interstitial lung disease: How does it differ from IPF? How should the clinical approach differ?

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Connective tissue disease-associated interstitial lung disease: How does it differ from IPF? How should the clinical approach differ?

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Abstract

The lung is frequently involved in connective tissue diseases (CTDs), although the frequency of lung manifestations varies according to the type of CTD. Interstitial lung diseases (ILD) are frequently seen in CTDs, particularly systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM) and rheumatoid arthritis (RA), accounting for a significant proportion of deaths. A large percentage of patients with CTD-associated ILD has limited and stable disease, not requiring treatment. However, a significant minority has severe and/or progressive disease, necessitating prompt initiation of treatment. CTD-ILD histological patterns include non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), diffuse alveolar damage (DAD) and lymphocytic interstitial pneumonia (LIP). NSIP is the most common pattern in all CTDs, except for RA, characterized by a higher frequency of UIP. ILD can present acutely or chronically, with acute presentations being more common in systemic lupus erythematosus and PM/DM. Idiopathic pulmonary fibrosis (IPF) is a progressively worsening ILD characterized by inflammation and fibrosis. The characteristic histological pattern of IPF is UIP. Interestingly, a UIP pattern is associated with a significantly better survival in CTD-related disease compared to the idiopathic variety. Prognosis in IPF is dismal, with a median survival since diagnosis of 2–3 years. No treatment regimen has been shown to improve survival in IPF. By contrast, although there have been only two randomized placebo-controlled trials investigating the effect of immunosuppressive treatment in SSc-associated ILD, clinical experience suggests that immunosuppressive drugs in CTD-related ILDs are capable of benefiting a significant proportion of patients, particularly those with certain histological patterns of disease. This review will essentially focus on CTD-associated ILD and will compare aspects of clinical presentation and management to those of IPF.

Keywords

connective tissue disease, interstitial lung disease, idiopathic pulmonary fibrosis, management, histological pattern

The lungs are frequently involved in connective tissue diseases (CTDs), resulting in significant morbidity and mortality. All components of the lung can be affected, including the interstitium, the large and small airways, the pleura and the pulmonary vasculature. A combination of patterns is frequently seen; indeed one of the features suggestive of an underlying CTD is the finding of abnormalities in more than one compartment (for example airways and interstitium) on imaging and/or histology. Despite the wide variety, there are certain patterns that occur more frequently in each

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Table 1. Pattern of respiratory involvement in connective tissue disease

	Airways	Pleura	PAH	Muscle	ILD	ILD pattern
SSc	−/+	−/+	+++	−	+++++	NSIP>>>UIP
RA	++++	+++	−/+	−	++	UIP>NSIP>OP=DAD
PM/DM	−/+	−	−/+	++	++++	NSIP=OP>DAD>UIP
Sjögren's	+++++	−/+	+	−/+	+++	NSIP>LIP>OP=UIP=DAD
SLE	−/+	++++	++	+	+	NSIP>DAD=LIP=OP=UIP

Abbreviations: SSc: systemic sclerosis, RA: rheumatoid arthritis, PM/DM: polymyositis/dermatomyositis, SjS: Sjögren's syndrome, SLE: systemic lupus erythematosus, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, OP: organizing pneumonia, DAD: diffuse alveolar damage, LIP: lymphocytic interstitial pneumonia.

Table 2. ATS/ERS diagnostic criteria for idiopathic pulmonary fibrosis (IPF)[1,a]

Major criteria	Minor criteria
Exclusion of other known causes of interstitial lung disease, including environmental exposures, connective tissue diseases and drug toxicities.	Age >50 years.
Abnormal pulmonary function tests consistent with restrictive and/or impaired gas exchange (increased A-aPO_2 with rest or exercise or decreased DLCO).	Insidious onset of otherwise unexplained dyspnoea on exertion.
Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT scans.	Duration of illness $\geq$3 months.
Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis.	Bibasilar inspiratory crackles (dry or 'Velcro' type in quality).

[a] In the absence of surgical lung biopsy, all major criteria and at least 3 minor criteria are required.

CTD; a rough estimate of the frequency of different compartment involvement is outlined in Table 1. CTDs are usually associated with autoantibodies, many of which are directed against nuclear components; the type of autoantibody present can be specific for a particular CTD, greatly aiding the diagnostic process. This review will essentially focus on CTD-associated interstitial lung disease (CTD-ILD) and will compare aspects of clinical presentation and management to those of idiopathic pulmonary fibrosis.

Lung involvement, and particularly interstitial lung disease (ILD), can be the first manifestation of a CTD, at times preceding extrapulmonary symptoms by several years. A careful history for connective tissue disease symptoms and a wide autoimmune screen in all patients who present with seemingly idiopathic ILD is therefore warranted. Up to 25% of ILD occurs in the context of an 'undifferentiated' connective tissue disease, characterized by signs and symptoms that are not specific for any of the described CTD entities but suggestive of an underlying autoimmune condition, thus making the distinction with the idiopathic interstitial pneumonias (IIPs) challenging.

Idiopathic pulmonary fibrosis (IPF), as the name suggests, is a fibrotic lung disease of unknown origin characterized by inflammation and fibrosis. The diagnosis of IPF is made when histology and/or CT imaging is consistent with a pattern of usual interstitial pneumonia (UIP; main features outlined in Table 2), in the appropriate clinical setting. In the absence of a surgical lung biopsy, the diagnosis can be confidently made when all major criteria and at least three minor criteria are met.[1] In particular, in the case of an HRCT pattern judged to be typical of IPF (peripheral, predominantly basal reticulation and honeycombing with little, if any, ground glass changes), the diagnosis is correct in >90% of cases,[2-4] such that a surgical biopsy is not justified in the appropriate clinical setting.

This review will focus on the most frequent CTDs: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma (SSc), Sjögren's syndrome (SjS), dermatomyositis/polymyositis (DM/PM) and mixed CTD (MCTD). The review will initially touch on a few issues valid for all CTDs, including the distinction between limited versus extensive ILD, lung function patterns and histological pattern nomenclature. A few general principles in the management of

CTD-associated ILD, also compared with IPF management, will be outlined following the section on the individual CTD entities.

Trivial versus significant ILD

ILD can occur in all of the CTDs, although its prevalence varies, with the highest frequency observed in systemic sclerosis (SSc) and the lowest in SLE. The routine use of chest high resolution computed tomography (HRCT), much more sensitive in detecting parenchymal changes than the plain chest radiograph (chest X-ray), has led to an increased detection of patients with interstitial involvement. However, many patients have clinically trivial disease with minimal impairment of lung function and limited progression. Therefore, identifying disease extent in a clinical context (i.e. trivial vs extensive) is crucial for appropriate management. Although bronchoalveolar lavage (BAL) is helpful in excluding infection, and identifying unusual cellular profiles (for example, a striking eosinophilia could raise possibility of a drug reaction), the issue of whether BAL cellular profiles provide prognostic information independently of disease severity is still debated.[5,6] Chest HRCT and lung function tests are the most useful in establishing the clinical significance of an ILD. Clear parameters which allow staging of ILD have only been developed for SSc-ILD[7] (discussed in the SSc section). Although a staging algorithm needs to be developed for ILD in the context of the other CTDs, as an approximate empirical guide, an average CT extent of <10% and/or a transfer coefficient for carbon monoxide (DLCO) >65% and/or forced vital capacity (FVC) >75% suggest limited disease, and a period of monitoring of lung function is likely to be useful to decide whether treatment is required.

In contrast to the variable rate of progression of CTD-ILD, with a substantial proportion of patients with limited and stable disease even without treatment, IPF is almost invariably a progressive disease, with a median survival since diagnosis of 2–3 years.[8] Identifying trivial disease in CTD-related ILDs is possible when systemic disease is diagnosed and provides an opportunity for conservative management. However, the fact that ILD can be the first presentation of a CTD, with systemic symptoms developing much later, can represent a diagnostic challenge. In contrast to CTD-ILD, IPF is a relentlessly progressive disease; therefore, treatment options should be considered early in the course of the disease. The fact that current treatment options have only a limited impact on the disease suggests the need to enroll patients with IPF in randomized controlled clinical trials, when possible.

Histological patterns

The 2002 ERS/ATS re-classification of the idiopathic interstitial pneumonias introduced non-specific interstitial pneumonia (NSIP: further subdivided into cellular and fibrotic NSIP) as a distinct pattern, in addition to usual interstitial pneumonia (UIP), diffuse alveolar damage (DAD), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis interstitial lung disease (RB-ILD).[8] The radiological and histological patterns defining each entity are briefly summarized in Table 3.

In the past, IPF was thought to be histologically and radiologically indistinguishable from connective tissue-related ILD, particularly systemic sclerosis.[9] However, studies performed after the ATS/ERS reclassification[8] have shown that, in contrast to the idiopathic interstitial pneumonias, where UIP is the most common pattern (and is diagnostic of IPF), the most frequent pathological pattern in CTD-ILD is NSIP, except for rheumatoid arthritis, which is characterized by a higher frequency of UIP[10,11] (Table 1). Furthermore, it is now clear that IPF has a significantly worse prognosis compared to the CTD-ILDs.[12-14]

The prevalence of the other less common patterns varies among the different CTDs. OP is most often seen in the context of polymyositis and rheumatoid arthritis (and of undifferentiated CTD, unpublished data). It can also be found in SjS and in SLE, whereas it is vanishingly rare in the context of SSc. A lymphocytic interstitial pneumonia pattern (LIP) is most often seen in the context of SjS, can be found in RA, but is rarely seen in the other CTDs. A diffuse alveolar damage pattern is most frequently seen in the context of RA, PM/DM, SLE or of an undifferentiated CTD,[15] while it is exceedingly rare in the context of SSc, with only a handful of case reports in the literature.[16,17] A diffuse alveolar damage pattern can also occur on a background of a fibrotic ILD, just as acute exacerbation can occur in IPF (DAD occurring on a background of UIP). Finally, with the exception of SSc-ILD, a combination of histological patterns is quite frequent in the context of CTDs (Figure 1), and should in itself raise the possibility of a 'forme fruste' of CTD even in patients who do not yet present with

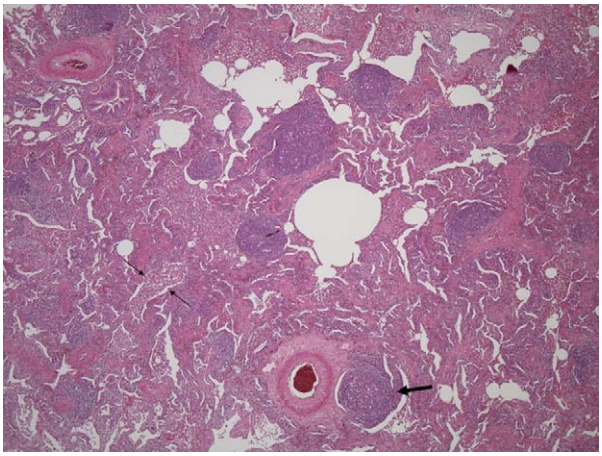

Figure 1. Surgical lung biopsy from a 45-year-old woman (ex-smoker), with interstitial lung disease on a background of undifferentiated connective tissue disease, showing a combination of follicular bronchiolitis (thick arrow) and desquamative interstitial pneumonia (thin arrows) with associated interstitial fibrosis (H&E ×20).

signs and symptoms suggestive of an underlying connective tissue disorder.

In SSc and in SjS, the relationship between CT findings and their histological counterparts appears to be similar to the IIPs,[18,19] but little data are available on the radiologic-pathologic correlations in RA, PM/DM and SLE.

Histological patterns and survival

In the idiopathic setting, studies have clearly shown that UIP (IPF) is characterized by a significantly worse survival than fibrotic NSIP, even after adjusting for disease severity.[2,20] The better survival seen in CTD-ILD compared to IPF could be related to a higher frequency of NSIP in the CTD group. However, in SSc-ILD[21] and in the other connective tissue diseases, survival does not seem to differ between UIP and NSIP,[14] and a UIP pattern in the context of a CTD has a significantly better survival than a UIP pattern in the idiopathic setting (IPF).[14] The reasons for this are unclear. Flaherty et al. reported a lower profusion of fibroblastic foci in nine CTD patients with a UIP pattern compared to IPF,[22] although others had not observed this.[23] In a larger study, comparing 39 patients with CTD-associated UIP pattern with 61 IPF/UIP patients, CTD-associated UIP biopsies had fewer fibroblastic foci, smaller honeycombing spaces, with higher numbers of germinal centers and higher inflammation scores than IPF/UIP biopsies.[24] Among pathological features, the honeycombing score was significantly associated with a worse survival, while germinal centres provided the best discrimination between CTD-UIP and IPF/UIP, with a marginal impact on survival. Interestingly, the subgroup of IPF with no clinical features of CTD, but positive autoantibodies, had histological features more similar to CTD-associated UIP than to IPF/UIP, although survival was no better than for auto-antibody negative IPF. Whether the lack of a survival difference between auto-antibody positive and negative IPF patients is related to the relatively small numbers involved will need to be clarified with future studies, as it would have obvious clinical management implications.[24] Rheumatoid arthritis-associated UIP may represent a possible exception to the better survival seen in CTD-UIP compared to IPF/UIP, as discussed in the specific RA section.

In conclusion, with the possible exception of RA, a distinction between a fibrotic NSIP and a UIP pattern in the context of a CTD does not provide prognostic separation. Therefore, a surgical lung biopsy is not needed in this context to guide management.

The value of histological patterns other than UIP or NSIP in providing prognostic separation within each connective tissue disease has not been formally evaluated. Anecdotally, an LIP pattern is associated with a good response to corticosteroids, with improvement and/or stabilization of disease. The spectrum of OP in the context of CTD is intriguing: although OP can be associated with reversibility on treatment (with or without relapses), OP in the context of CTD is frequently associated with interstitial fibrosis, which histologically often corresponds to an overlap between NSIP and OP. Diffuse alveolar damage is usually associated with a life-threatening acute or sub-acute presentation, often in association with OP in the context of CTDs. Minimal data exists regarding the frequencies of the various subtypes of OP in CTDs, and of their prognostic significance.

Lung function

The interpretation of lung function in the context of CTDs can be complex, again because of the variety of compartments potentially involved in the same patient. To summarize, in all CTDs, there can be four main mechanisms leading to lung function impairment:

a) interstitial abnormalities: these are associated with a restrictive pattern, with proportional reduction in FVC and forced expiratory volume in the first

second (FEV1), and concomitant reduction in the transfer coefficient for carbon monoxide (DLCO). DLCO is the most sensitive marker of ILD,[25] and is the first parameter to be reduced in the early or limited stages of the disease;

b) pulmonary vascular abnormalities; when present in isolation (i.e.: absent or very limited ILD), these are associated with reduced DLCO and KCO (DLCO/alveolar volume), but normal or near normal lung volumes;

c) extrapulmonary restriction caused by respiratory muscle involvement and/or skin changes (in diffuse scleroderma), leading to reduced lung volumes, but normal or near normal DLCO and supranormal KCO;

d) smoking-related emphysematous and airway changes, which tend to attenuate the effects of the interstitial abnormalities on the lung volumes, but are associated with a greater reduction in DLCO and KCO than expected from ILD alone, with spurious preservation of lung volumes. This pattern is particularly frequent in IPF and in RA-associated ILD.

These abnormalities may present in isolation, and be relatively simple to interpret, or may present in combinations of varying degrees, with difficulties in teasing out the relative contribution of each to functional impairment. A disproportionate reduction in DLCO when compared to lung volumes and/or extent of ILD on CT should always suggest the possibility of pulmonary vascular disease (in the absence of concomitant emphysema) prompting assessment of pulmonary hypertension.[26] An extrapulmonary pattern of restriction secondary to chest wall skin thickening or to muscle involvement can be seen in combination with interstitial changes in diffuse cutaneous SSc, in PM/DM and in mixed CTD; pointers include a greater reduction in lung volumes than in DLCO.

Systemic sclerosis

SSc is defined by the presence of major (skin thickening proximal to metacarpo-phalangeal joints) and minor (sclerodactyly, oesophageal involvement and lung fibrosis) criteria. Classically, it is further subdivided into diffuse and limited SSc, according to extent of skin disease (diffuse SSc: skin thickening proximal to elbows and knees), with different associations with internal organ involvement and autoantibody subsets.

Autoantibody subsets

Anti-nuclear antibodies (ANA) are found in the majority of SSc patients. The three main autoantibodies, with high specificity for SSc, include antibodies against topoisomerase (ATA or anti Scl-70), anticentromere antibodies (ACA) and anti-RNA polymerase III (ARA). These tend to be mutually exclusive and are linked to distinct disease patterns, although their role in pathogenesis remains debated. There is however quite a large proportion of patients who are negative for all three main autoantibody subsets. ATA antibodies are strongly associated with ILD.[27] By contrast, ACA positivity is strongly predictive of the absence of significant lung fibrosis but is associated with development of pulmonary hypertension late in the course of the disease.[27] ACA is more frequent in Caucasians (20%–35%) and is very strongly associated with limited disease in the context of a CREST syndrome (calcinosis, Raynaud's, oesophageal involvement, sclerodactyly and teleangectasias). The other major autoantibody, ARA, is associated with diffuse skin disease and renal crisis, whereas it is infrequently associated with significant lung fibrosis.[27]

Although almost all patients with ATA have some degree of interstitial lung involvement, at least half of SSc-ILD patients are ATA negative. While Th/To antibodies, found in a small group of patients, are linked to lung fibrosis with disproportionate pulmonary hypertension, a large proportion of SSc patients with lung fibrosis have no specific antibody. It is possible that further research will uncover other autoantibodies as markers of ILD.

Interstitial lung disease

Prevalence. SSc is the CTD with the highest frequency of ILD, ranging from 40% to 80% depending on method of ascertainment. The frequency of ILD varies according to ethnicity, autoantibody subsets and skin disease extent.[28,29]

Morphology and BAL. As mentioned previously, the great majority of SSc-ILD biopsies are characterized by an NSIP pattern, as confirmed by several recent studies, including the largest one published by Bouros et al. on 80 SSc-ILD patients.[21] HRCT findings mirror this, with features characterized by ground glass pattern, reticulation and limited honeycombing, which closely resemble imaging features of patients with idiopathic NSIP (Figure 2).[19] As mentioned above, in contrast with the idiopathic setting, a UIP pattern in the

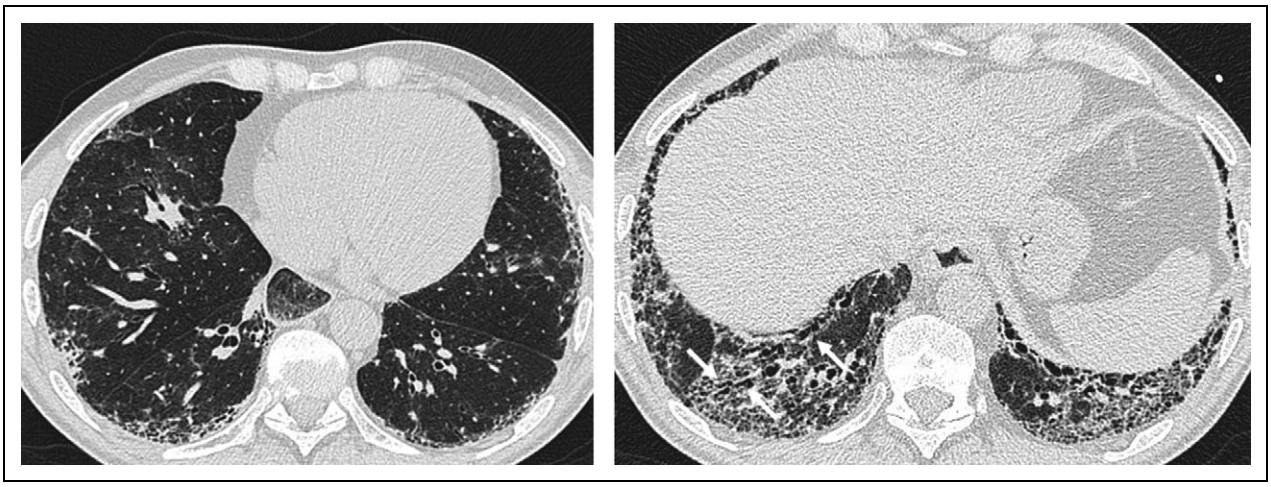

Figure 2. CT of a 65-year-old man with Scleroderma-associated interstitial lung disease, showing predominantly basal ground glass admixed with reticulation and obvious traction bronchiectasis (arrows), in keeping with an established fibrotic non-specific interstitial pneumonia (NSIP) pattern.

context of SSc does not appear to be associated with a worse prognosis compared to NSIP.[21] Lung biopsies are thus not recommended for routine diagnosis of SSc-ILD, unless there are unusual clinical or radiological features. Interestingly, non-UIP/non-NSIP patterns are quite rare in the context of SSc; in particular, a subacute and/or acute presentation of life-threatening illness characterized by an imaging/histological pattern of DAD is exceedingly rare in SSc, as is a pattern of OP. Furthermore, in contrast with the other CTDs, the pattern of involvement in SSc tends to be limited to the interstitium with/without vascular involvement, whereas pleural and airways disease are seen only rarely.

Management. Although most SSc patients have some degree of ILD, the majority have relatively limited disease, which remains stable without treatment. However, a proportion of SSc patients have significant and/or progressive ILD, with a tendency to progress if left untreated. The challenge lies in rightly targeting the latter group for treatment, while avoiding unnecessary medication toxicity in the former. Markers of likelihood of future progression include extent of disease on CT, level of functional impairment, documented recent functional decline, early disease and a short interval between diagnosis of SSc and onset of respiratory symptoms.[7,30] Autoantibody subsets are also useful; ACA positivity is extremely unlikely to be associated with severe progressive ILD, whereas ATA positivity suggests the need for close monitoring of lung function, although it is unclear whether it is also a marker of inherently more progressive lung fibrosis.[31]

A staging system based on assessment of disease severity to identify SSc-ILD associated with a poorer outcome has recently been proposed by Goh and co-authors.[7] In brief, patients with a significantly worse survival can be identified by a semi-quantitative rapid assessment of extent of disease on CT, integrated, if necessary, by lung function. Patients are classified as having extensive or limited disease depending on whether CT extent is deemed to be above or less than 20%, respectively. If estimation of this threshold is uncertain, the distinction between extensive and limited disease is made according to whether FVC is lower or higher than 70% of predicted, respectively. The degree of prognostic separation provided by this simple staging system was observed to be greater than either CT extent or lung function impairment used in isolation. The authors argue that this staging system should be used to make prognostic statements and as a stratification tool in patient selection for clinical trials. As the study included both treated and untreated patients, it cannot be used to define thresholds for initiation of treatment. Clearly, as a shorter survival was observed in patients with 'extensive' disease, despite ongoing treatment, this should be started before such a threshold is reached, although further studies are needed to better define this.

Clearance of inhaled technetium-labeled diethylenetriamine pentaacetate (99mTc-DTPA), a marker of epithelial damage and permeability, has also been associated to likelihood of progression both in

SSc-ILD and in idiopathic ILD,[32] although larger studies correcting for disease severity are needed. As 99mTc-DTPA clearance is not widely available, serum biomarkers of lung epithelial cell damage and replication such as KL-6 (currently available only in Japan) and surfactant protein A and D[33,34] are currently investigated as promising markers of inherently progressive disease. Although further studies are needed, it may be possible to integrate epithelial damage markers in a treatment algorithm to identify patients in the early stages of disease who are likely to progress if left untreated.

SSc-ILD is the only CTD-associated ILD for which placebo-controlled randomized trials have been performed. Even prior to the two randomized placebo controlled trials, the Scleroderma Lung Study (SLS)[35] and the fibrosing alveolitis scleroderma trial (FAST),[36] there had been several uncontrolled studies suggesting that intravenous or oral cyclophosphamide +/- corticosteroids were effective in reversing ongoing functional decline at least in a proportion of SSc-ILD patients. Both the SLS study comparing oral cyclophosphamide (2 mg/kg) against placebo over 1 year of treatment and the FAST trial comparing monthly intravenous cyclophosphamide (600 mg/m^2) for 6 months, followed by oral azathioprine for the remaining 6 months, found similar, if small, differences in the primary outcome variable, FVC% change after 1 year of treatment, compared to placebo. The advantages of using intravenous rather than oral cyclophosphamide include lower rates of bone marrow toxicity, severe infections and gonadal failure (likely to be secondary to the substantial reduction in the cumulative dose used with the intravenous route).[37] With regards to the need for longer term immunosuppression, SLS patients were followed up for a further year off treatment. The lung function advantage in cyclophosphamide compared to placebo-treated patients was completely lost after 12 months from discontinuing cyclophosphamide, suggesting the need for ongoing immunosuppression to maintain disease stability.[38]

In view of the cumulative risk of bladder and haematological malignancies seen with long-term use of cyclophosphamide, less toxic alternatives are needed. Although there are no controlled studies, azathioprine is often used in clinical practice as maintenance treatment following intravenous cyclophosphamide. Unfortunately, approximately 20% of patients have to stop azathioprine because of significant side effects, including liver function abnormalities, severe gastro-intestinal side effects and, less frequently, severe leukopenia. Mycophenolate is generally better tolerated than azathioprine and represents a promising less toxic alternative to cyclophosphamide in SSc-ILD, as highlighted by several small retrospective trials, suggesting its effectiveness in preventing further decline in patients with progressive disease.[39-41] A large NIH-funded randomized placebo-controlled trial of mycophenolate against cyclophosphamide is currently enrolling patients and is expected to be completed in 2012.

In conclusion, in SSc-ILD requiring treatment, current recommendations include low-dose oral corticosteroids (prednisolone 10 mg od) and monthly intravenous cyclophosphamide (600 mg/m^2) for 6 months, followed by either +/− dose steroids oral azathioprine or mycophenolate. High-dose corticosteroids (>10 mg prednisolone) should be avoided in SSc in view of the significant risk of renal crisis.

Pulmonary hypertension

This review will only briefly touch on pulmonary arterial hypertension (PAH) in SSc. PAH is estimated to occur in 12%–15% of patients with SSc, and together with ILD, is now the main cause of death in SSc.[42]

SSc-associated PAH (SSc-PAH) can occur as an isolated form, in the absence of significant interstitial lung involvement. Isolated PAH tends to occur late in the course of the disease and is associated with a long history of Raynaud's phenomenon, limited cutaneous involvement and anti-centromere antibody positivity.[43,44] SSc-PAH can also occur in the context of ILD, to a degree that may or may not be proportionate to the severity of the parenchymal disease, although very little information on the relative frequencies of isolated PAH vs PAH occurring in association with ILD is available in the literature.

Although SSc-PAH appears to have a worse prognosis than other forms of PAH including idiopathic PAH,[45-47] current treatment with anti-PAH agents, including endothelin-1 receptor antagonists,[48-50] phosphodiesterase type 5 inhibitors[51] and prostanoids,[52,53] appears to be associated with significant short-term improvement in exercise tolerance and pulmonary haemodynamics[48,49,54,55] and possibly an improved SSc-PAH survival. Compared to the pre-treatment era 1 year survival of 50%–55%,[45,56] current 1- and 2-year survival rates have been estimated, respectively, at 81% and 71%, by Williams et al.,[55] 86% and 73% by Mukerjee et al.[57] and at 80% and 56% by Launay et al.[58] The lower 2-year survival rates reported by Launay may be secondary to the inclusion of patients with

Table 3. Classification of histological and radiological patterns developed for idiopathic interstitial pneumonias, applied to connective tissue disease-associated interstitial lung disease[8]

Pattern	Histology	CT features
UIP	Subpleural and peripheral fibrosis. Temporal and spatial heterogeneity. Scattered *fibroblastic foci* and honeycombing are key features.	Basal, subpleural reticulation and honeycombing; traction bronchiectasis; little, if any, ground-glass attenuation.
NSIP	Uniform interstitial involvement by variable degrees of fibrosis and inflammation. Honeycombing is rare.	Bilateral patchy ground-glass opacities admixed with reticulation and traction bronchiectasis / bronchiolectasis. Little or no honeycombing. Usually, predominantly basal.
OP	Connective tissue plugs within small airways and air spaces (Masson bodies). In its 'pure' form, little or no inflammation or fibrosis in the surrounding interstitium.	Airspace consolidation, with a predominantly basal/ peripheral or peri-bronchovascular distribution. Bands with air bronchograms and a perilobular pattern can also be seen.
DIP	Extensive macrophage accumulation within the distal air spaces. Mild interstitial involvement	Patchy ground-glass opacities. Microcystic change can be seen within the ground-glass. Basal, peripheral distribution frequent.
LIP	Bronchiolocentric lymphoid tissue hyperplasia.	Ground-glass attenuation is the predominant finding, with thin-walled cysts frequently present. Lung nodules and septal thickening may also be seen
RB-ILD	Bronchiolocentric macrophage accumulation. Mild bronchiolar fibrosis.	Centrilobular nodules, ground glass opacities. Diffuse or upper lung distribution
DAD	In the acute phase: hyaline membranes, edema. In the organizing phase: airspace and interstitial organization.	Acute phase: diffuse ground-glass opacities and consolidation in dependent areas. Organizing, phase: reticular pattern, traction bronchiectasis and architectural distortion

Abbreviations: DIP: desquamative interstitial pneumonia, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, OP: organizing pneumonia, DAD: diffuse alveolar damage, RB-ILD: respiratory bronchiolitis interstitial lung disease, LIP: lymphocytic interstitial pneumonia.

ILD in their cohort of patients with SSc-PAH; this group is believed to have a worse prognosis and response to treatment, although current data are limited.

The reasons for the reduced effectiveness of treatment in SSc-PAH compared to other forms of PAH including idiopathic PAH are unclear, although increased frequency of veno-occlusive disease and/ or concomitant cardiac disease may play a role.[46,59-61]

Current efforts are aimed at earlier non-invasive identification of the development of pulmonary hypertension, so that earlier institution of treatment can prevent vascular remodelling. In this regard, serum brain natriuretic peptide (BNP) and *N*-terminal pro-brain natriuretic peptide are showing promise as independent predictors of subsequent development of SSc-PAH.[62]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common of the connective tissue diseases, with a prevalence of 1%−2%, and a female: male ratio of 3:1. RA is characterized by an erosive inflammatory polyarthropathy, mostly affecting the distal joints. Extra-articular manifestations include subcutaneous nodules, pericarditis, splenomegaly, skin ulceration, increased frequency of atherosclerotic artery disease and a variety of pleuro-pulmonary abnormalities. The diagnosis is suggested by the typical early morning joint stiffness and pain associated with objective signs of arthritis and erosions seen on X-ray and suggestive serological tests including a positive rheumatoid factor (Table 4). Anti-cyclic citrullinated peptide antibodies (CCP) are highly specific for RA, but only moderately sensitive, and are associated with more severe joint disease.[63] Further, rheumatoid factor and anti-CCP antibodies predict development of rheumatoid arthritis in asymptomatic or minimally symptomatic individuals[64,65] and have been described as the sole sign of underlying connective tissue disease in patients with isolated ILD and a history of smoking.[66]

Lung disease accounts for a significant proportion of deaths in RA, second only to cardiac disease.[67] Rheumatoid arthritis is arguably characterized by the

Table 4. Criteria for the diagnosis of rheumatoid arthritis (RA)

Diagnostic criteria for rheumatoid arthritis[a]
Morning stiffness in or around the joints lasting at least one hour
Arthritis (soft tissue or swelling, not only bony overgrowth alone) of three or more joints (PIP, MCP, wrist, elbow, knee, ankle, MTP)
Arthritis of wrist, MCP or PIP joints
Symmetrical arthritis
Rheumatoid nodules (subcutaneous nodules over bony prominences, extensor surfaces, or iuxta-articular regions)
Raised serum rheumatoid factor
Radiographic abnormalities of hand or wrist in keeping with RA (erosions or unequivocal bony calcifications in or close to involved joints)

[a]At least four of the above criteria have to be met for classification purposes.

Table 5. Respiratory manifestations of rheumatoid arthritis

Respiratory manifestations (frequency)
Interstitial lung disease (5%–58%)
Bronchiectasis (30%)
Follicular bronchiolitis
Constrictive bronchiolitis
Rheumatoid nodules (0-37%)
Pleural disease (up to 50%)
Vasculitis (rare)
Pulmonary arterial hypertension (clinically obvious PAH rare)

most heterogeneous patterns of lung involvement among CTDs, both between patients and within the same individual.[68] Airway, pleural, vascular and parenchymal involvement can occur in RA patients, as well as abnormalities indirectly associated with RA such as pulmonary opportunistic infections and drug-induced lung disease. All of the pleuropulmonary manifestations in RA are more common in males. Table 5 lists the different patterns of lung involvement and estimated frequencies.

Interstitial lung disease

ILD affects men twice as commonly as women, in line with other lung manifestations of RA. The prevalence of ILD ranges widely from 5% to 58%, depending upon method of ascertainment and selection criteria.[69-71] Smoking is a significant risk factor for ILD. An odds ratio of 3.8 for ILD was observed in RA patients with a smoking history >25 pack years.[72]

As mentioned in the introductory section, in contrast to the other CTDs, the most frequent histological pattern in RA appears to be UIP, followed by NSIP (cellular or, more commonly, fibrotic NSIP).[73] There is evidence suggesting that in RA, a UIP pattern may be associated with a worse survival than fibrotic NSIP, in contrast with the other CTDs. Park et al compared survival between UIP and NSIP patterns both in idiopathic and in CTD-associated disease, and reported that RA-associated UIP tended to have a worse survival than non-RA connective-tissue-associated NSIP or UIP, although the trend was no longer significant once baseline lung function impairment was taken into account.[14] However, this study, although large, included only 28 patients with RA-ILD. In a recent retrospective study of 82 patients with RA-ILD, Kim et al. reported a worse survival for patients with a UIP pattern on HRCT.[74] Furthermore, estimated survival in RA-associated UIP did not differ significantly from that of IPF.[74]

A pattern of diffuse alveolar damage/acute interstitial pneumonia is an infrequent, but dramatic, ILD manifestation of RA, which can occur in a previously normal lung, or as the presenting pattern of a previously undiagnosed ILD. The characteristic CT pattern of diffuse alveolar damage includes widespread ground glass with/without areas of dependent consolidation. However, a similar pattern could represent opportunistic or viral infection, or acute heart failure. If clinically feasible, a bronchoscopy with collection of microbiology samples is crucial to exclude infection, while ancillary clinical signs and an echocardiogram are useful to exclude heart failure. OP with/without interstitial lung fibrosis is also seen in patients with RA, as is an LIP pattern, and, infrequently, a DIP pattern.

Management of RA-associated ILD. Little is known of the responsiveness to treatment of rheumatoid-associated ILD and whether there are fundamental differences in the response to immunosuppression between RA-associated UIP and fibrotic NSIP, as in to their idiopathic counterparts. The fact that a UIP pattern in the context of RA appears to carry a worse prognosis could suggest the need for histological confirmation in doubtful cases, as recently proposed by Kim et al.[73]

In the absence of any randomized controlled trials, treatment of RA-ILD is empirical. Patients with a

potentially reversible pattern such as OP are treated with high doses of corticosteroids (either oral or intravenous methylprednisolone). Immunosuppressive agents, including cyclophosphamide, azathioprine or mycophenolate are also used either as corticosteroid sparing agents or in patients not responding to corticosteroids alone. On a practical basis, in patients showing evidence of ongoing, but gradual, progression with either a UIP or a fibrotic NSIP pattern, the most frequently used regimen would be oral prednisolone, in addition to azathioprine or mycophenolate, although a randomized trial comparing the effects of immunosuppression between UIP and fibrotic NSIP patterns is needed. Whether *N*-acetylcysteine increases the likelihood of stabilization in addition to prednisolone and azathioprine in RA-associated UIP, similar to IPF, is not known. Intravenous cyclophosphamide can be considered in rapidly progressive fibrotic NSIP or UIP, although evidence for its effectiveness is lacking. In view of its poor prognosis, a pattern of diffuse alveolar damage presenting with rapidly progressive respiratory failure requires aggressive therapy, with high dose intravenous methylprednisolone +/- intravenous cyclophosphamide. Salvage rituximab therapy can be considered in particularly severe presentations and/or in unresponsive disease.

Drug-induced ILD in RA. Most of the drugs used for the treatment of RA joint disease can be associated with lung reactions, with clinical and imaging features that can be indistinguishable from RA-associated lung disease. Time of onset of respiratory symptoms in relation to the start of the drug and the tendency towards improvement of the lung disease on stopping it (+/- treatment with corticosteroids) are potential clues, although very delayed reactions or continued progression despite discontinuing the drug are also possible. Distinguishing between drug-induced pneumonitis and infection can be difficult, and BAL sampling for microbiology cultures should be performed, if at all possible. At times it is necessary to resort to a transbronchial or a surgical lung biopsy; however, although histology can be helpful in excluding unusual infections, it is seldom helpful in distinguishing between RA-associated ILD and a drug reaction, as features such as granulomas and increased numbers of tissue eosinophils can be found in both.

Methotrexate (MTX) is among the most commonly used disease modifying agents in RA and is associated with lung reactions with a frequency ranging from 0.3% to 11.6%.[75] Pre-existing ILD is a recognized risk factor.[76,77] Although most cases of methotrexate lung will occur within 1 year of starting treatment, there is no clear correlation between development of MTX lung and dose or duration of treatment. Most commonly, MTX is associated with a subacute clinical presentation occurring over a few weeks with cough, fever and shortness of breath, BAL lymphocytosis +/- eosinophilia +/- peripheral eosinophilia, radiological infiltrates and a cellular interstitial pneumonitis with granulomas on histology. Good responses are generally achieved with drug cessation plus corticosteroid treatment.[75] Other patterns include acute lung injury/DAD pattern with explosive, life-threatening presentation, difficult to distinguish from RA-associated acute lung injury. OP and a fibrotic NSIP pattern have also been described.[75] Most cases of MTX-induced lung toxicity have a good prognosis, although continued progression of interstitial fibrosis and subsequent death have been reported in approximately 10% and seem more frequent in patients with pre-existing ILD.[78]

Leflunomide has been associated with lung reactions in 1% of cases, most frequently an acute lung injury/DAD pattern, either when used as monotherapy or when added to MTX[79,80]; case reports of secondary alveolar proteinosis[81] and vasculitis associated with acute pulmonary haemorrhage, with rapid resolution on stopping the drug and treatment with high-dose corticosteroids,[82] have been described.

Gold salts are associated with lung toxicity in approximately 1% of cases; described patterns include diffuse alveolar damage, OP and fibrotic NSIP.[83]

Sulfasalazine and related compounds are used in RA, in other CTDs, and in inflammatory bowel disease. Sulfasalazine has been associated with pulmonary toxicities, mostly presenting with cough and/or fever. The most frequently described pattern is pulmonary eosinophilia, although OP and unspecified interstitial inflammation with or without fibrosis have also been reported.[84] The great majority of cases reported in the literature, including two patients with rheumatoid arthritis,[85] improved on stopping the drug with/without a short course of corticosteroid treatment.[84] Importantly, there were two deaths from respiratory failure out of three reported cases, all with ulcerative colitis, in whom sulphasalazine was not discontinued.

TNF-antagonists have been associated with development of rapidly progressive respiratory failure in several cases in the literature, particularly in older patients and/or those with pre-existing ILD[86];

non-infectious granulomatous lung disease has also been associated with TNF-antagonists.[87]

Rituximab, a monoclonal antibody against the pan-B cell marker CD20, originally developed for the treatment of B cell lymphomas, can be used as a second-line agent for RA joint disease in patients failing TNF antagonists. Rituximab-associated ILD is quite rare, with a reported rate of <0.03% in a study of 540,000 (mostly cancer) patients.[88] Although the majority of reported lung reactions regressed on discontinuation of treatment +/- corticosteroid treatment, two cases of fatal progressive ILD are reported in patients who had received rituximab in association with multi-chemotherapy regimens.[89] To our knowledge, there has been only one report of rituximab-associated lung toxicity (OP) in a patient with RA, with rapid response to stopping treatment and a brief course of corticosteroids.[90]

In summary, a thorough drug history is crucial in all cases of RA-ILD and indeed in all CTDs. An acute/subacute presentation occurring shortly after the introduction of a new treatment will be easier to ascribe to a drug than a chronic form, where the causative relationship may never be definitively proven. In view of the greater frequency of lung toxicity in patients with RA and pre-existing lung disease, we recommend avoiding, if at all possible, drugs associated with relatively high rates of lung toxicity and/or severe reactions, including methotrexate, leflunomide and TNF antagonists in patients with significant ILD. A detailed and useful categorization of all the drugs known to be associated with lung toxicity can be found online on pneumotox.com.

Polymyositis and Dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are relatively rare idiopathic systemic inflammatory diseases affecting striated muscles and other internal organs, particularly the lungs.[91] Diagnostic criteria for PM/DM include symmetrical proximal muscles weakness, raised serum muscle enzymes, muscle biopsy consistent with myositis, characteristic electromyographic alterations, and, for DM, typical cutaneous manifestations (heliotrope rash, Gottron's sign).[92,93] As PM/DM often occurs in overlap with other CTDs, more recent classification criteria have been suggested, which take into account the high frequency of overlap myositis with clinical and/or autoantibody features of other CTDs.[94] Although rare, amyopathic dermatomyositis (typical cutaneous findings but no myositis) can also occur.[95,96] Respiratory involvement is a major cause of morbidity and mortality in PM/DM[97-103] and is detectable in 30%–66% of patients.[104-106] PM/DM-associated lung involvement may manifest as ILD and/or as a consequence of respiratory muscle weakness leading to hypoventilation or, less frequently, aspiration pneumonia.

Interstitial lung disease

ILD is the most frequent respiratory complication in PM/DM. The reported prevalence varies widely, depending on methods of ascertainment and patient selection.[100,102,105,107-111] In a recent series, Fathi and colleagues report a prevalence of 78% in 23 consecutive Caucasian patients diagnosed with DM/PM referred to a rheumatological centre,[112] when any interstitial disease on HRCT and/or reduction in lung function were used as criteria. Such a high prevalence is likely to be related to referral selection bias and sensitive screening tests such as HRCT, and highlights the issue of distinguishing between trivial and significant ILD mentioned in the general section.

Apart from trivial asymptomatic ILD,[107,110] two main patterns of clinical presentation are seen[97-99]: (a) rapidly developing dyspnoea and pulmonary infiltrates (over a few weeks-months), with frequent evolution towards respiratory failure; this clinical presentation usually corresponds morphologically to a DAD pattern with variable overlap with OP and/or NSIP. A DAD pattern corresponds to diffuse ground-glass opacities and extensive consolidation on CT (Figure 3),[102,111,113,114] and is frequently associated with a poor prognosis and (b) an insidious onset of dyspnoea and radiological abnormalities, the most common pattern. Although features consistent with fibrotic NSIP are the most frequently described pattern in PM/DM both on CT (ground glass admixed with reticulation with little if any honeycombing) and biopsy,[68,108,115,116] OP is also frequently described,[117-119] more than in other CTDs,[68] often presenting in association, or preceding the development of fibrotic changes (Figure 4).[68,116,117] A UIP pattern can also be observed but is less frequent. Lung biopsy is not routinely used in the evaluation of patients with PM/DM. However, bronchoscopy with BAL +/- transbronchial biopsies for microbiological sampling may be needed in patients on immunosuppressive treatment to exclude infection.

Clinical and laboratory data

Respiratory manifestations in the context of PM/DM may develop after, concomitantly or before the onset

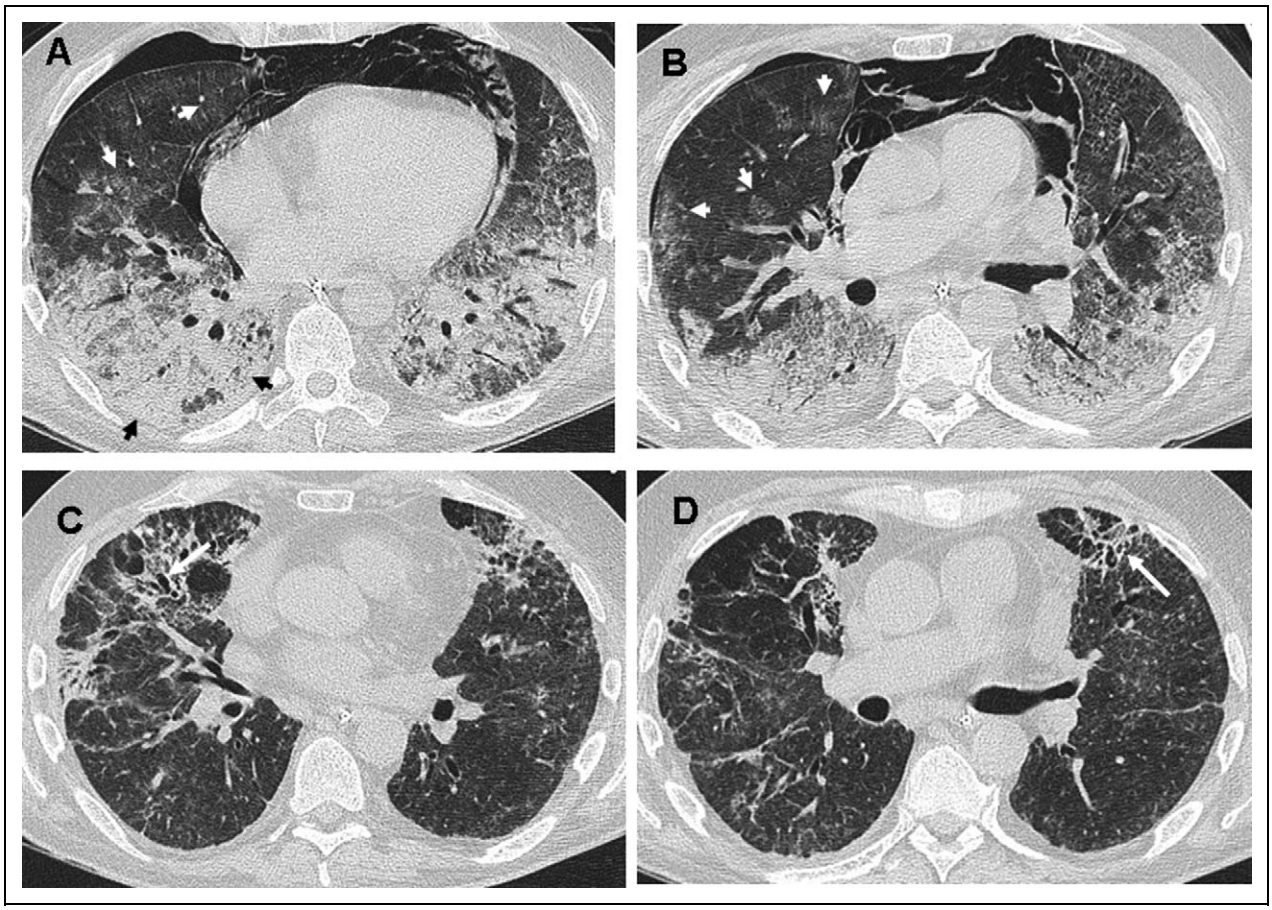

Figure 3. CT of a 49-year-old man with dermatomyositis with rapid onset respiratory failure: A-B: extensive consolidation (short black arrows) in the dependent lung with widespread patchy ground glass (short white arrows) anteriorly, consistent with diffuse alveolar damage (DAD)/ organizing pneumonia (OP). A right pneumothorax and a pneumomediastinum are present. C-D; after 2 months of ventilation and intensive immunosuppression, there is resolution of most of the consolidation, with residual reticulation and traction bronchiectasis (long white arrows) consistent with established fibrosis. The fibrosis is more conspicuous anteriorly, a feature of ventilator-associated damage

of muscle and skin changes.[98,110,120] Arthritis/arthralgia and older age (>45) are significantly associated with ILD.[102,110] Antibodies against aminoacyl-tRNA synthetases (anti-synthetases) have been tightly linked to ILD. The presence of one of the anti-synthetases, together with polymyositis, arthritis and ILD, is the hallmark of the anti-synthetase syndrome,[121] a clinical entity in which ILD is responsible for a 40% excess mortality.[121] Raynaud's phenomenon, fever and 'mechanic's hands' are other manifestations of this syndrome.[121,122] Anti-histidyl-tRNA synthetase (Anti-Jo1) is the most common anti-synthetase, detected in 25%−40% of patients with PM/DM[91,123,124] and in 30%−75% of the ILD subgroup.[100,102,105,109,115] Other known anti-synthetase antibodies include anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-KS and anti-Wa.[120,121,124] The reliability of this association is underlined by the link between anti-synthetase positivity and ILD even in the absence of myositis.[120,125] Similarly to other ILDs with and without CTDs, markers of epithelial cell damage/regeneration, including KL-6,[126,127] SP-D[127,128] and CK-19[129] have been reported as promising predictive markers of PM/DM associated-ILD. BAL neutrophilia has been associated with a poor outcome, although whether this simply reflects severity and/or a DAD pattern has not been clarified.[100,110]

When ILD is the sole pulmonary manifestation of DM/PM, lung function is characterized by a restrictive pattern and reduced DLCO; the pattern can be more complex when there is concomitant respiratory muscle involvement (see initial section on lung function). Respiratory muscle inflammation is associated with reduced lung volumes when muscle strength is less

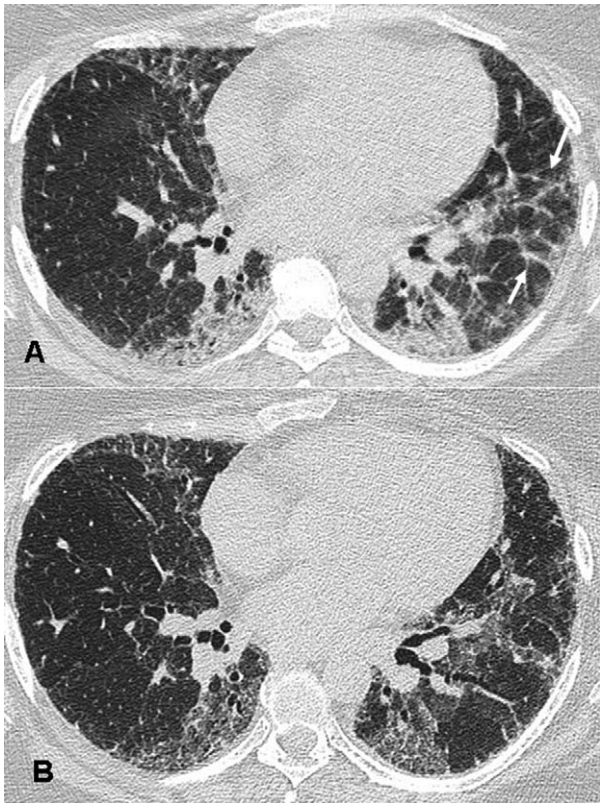

Figure 4. CT of a 54-year-old woman with polymyositis showing; A – patchy consolidation and perilobular pattern (arrows); B – four months later, following start of immunosuppressive treatment, the consolidation has been replaced by fine reticulation and distortion, in keeping with established fibrosis. The perilobular pattern in the left lung has resolved. This evolution is consistent with fibrosing organizing pneumonia.

than 50% of normal.[26] Reduced maximal respiratory pressures are hallmarks of myopathic restrictive disease,[109,130,131] although their normality does not exclude respiratory muscle involvement.

The risk of malignant tumours is notably increased in DM and less significantly increased in PM,[91,97] with a standardized index ratio for lung cancer of 5.9 and 2.8 for DM and PM, respectively.[132] Therefore, screening for occult neoplasm with thoracic-abdominal CT scan, mammography and pelvic ultrasound is advised.

Therapy. As for the other CTDs (except for SSc), the lack of randomized clinical trials means that no definite recommendation for PM/DM-associated ILD therapy is available. High dose oral prednisolone is often the first-line drug in myositis-associated ILD.[109,110,115,133] In rapidly progressive disease, high-dose intravenous treatment with methylprednisolone (1 g for 3 consecutive days) is often used. In patients with significant ILD, it is usual to add an oral immunosuppressant from the start, in view of the likelihood of disease progression in the case of undertreatment. The drugs most frequently used are azathioprine and mycophenolate, although others including cyclosporine, hydroxychloroquine, tacrolimus and methotrexate are also reported.[97,100,104,109,110,125,133,134] In severe rapidly progressive cases, intravenous cyclophosphamide is used either concomitantly or shortly after intravenous methylprednisolone, in the attempt to rapidly gain control of the disease.[110,133,134] Anti-CD20 therapy (rituximab) is emerging as a promising treatment in patients who have failed traditional immunosuppression and has been found to be successful in small case series/case reports both in the chronic ILD form and in the explosive DAD presentation.[135,136] However, further studies are needed to assess its efficacy and long-term safety. Respiratory muscle involvement has been reported to respond to immunosuppressive therapy and/or intravenous immunoglobulin.[109,137]

Sjögren's syndrome

Sjögren's syndrome (SjS) is an autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, which can be associated with extraglandular manifestations. SjS is classified as primary SjS (pSS), when it occurs in isolation, and secondary SjS (sSS), when it occurs in association with other CTDs, most commonly RA, SLE and SSc.[138] The primary form is associated with more severe disruption of exocrine function and more extraglandular manifestations, including renal tubular disorders, neurological manifestations and vascular disorders such as Raynaud's phenomenon and vasculitis.[139] Considering the vague nature of SjS symptoms, the fairly variable diagnostic criteria and the uncertainty added by the coexistence of other CTDs, a clear differentiation between the two entities can be difficult.[140-142]

According to the updated criteria proposed by the American-European Consensus Group, listed in Table 6, the presence of anti-nuclear antibodies against ribonucleoproteins Ro/SSA and/or La/SSB is mandatory, unless a compatible salivary gland biopsy, characterized by focal lymphocytic sialoadenitis, is available.[138] Other serological non-specific markers include polyclonal hypergammaglobulinemia, raised ESR and other non-SjS specific autoantibodies.[143]

Table 6. Diagnostic criteria for Sjögren's syndrome[138]

Diagnostic criteria for SjS [a]	
(I) Ocular symptoms	Dry eyes, sensation of sand, frequent use of tear substitutes
(II) Oral symptoms	Dry mouth, swollen salivary glands, drinking more liquids helps with dry food
(III) Ocular signs	Positive Shirmers's test, high ocular dryness score
(IV) Histopathology	Focal lymphocytic sialoadenitis in minor salivary glands
(V) Salivary gland involvement	Positive result for any of the following tests: unstimulated whole salivary flow, parotid sialography, salivary scintigraphy
(VI) Autoantibodies	Detection of antibodies to Ro(SSA) or La(SSB)

[a] To reach a diagnosis of SjS one of the following criteria has to be satisfied: (a) any four of the six listed items, provided either IV or VI is positive; (b) any three of the four objective criteria items (III, IV, V, VI)

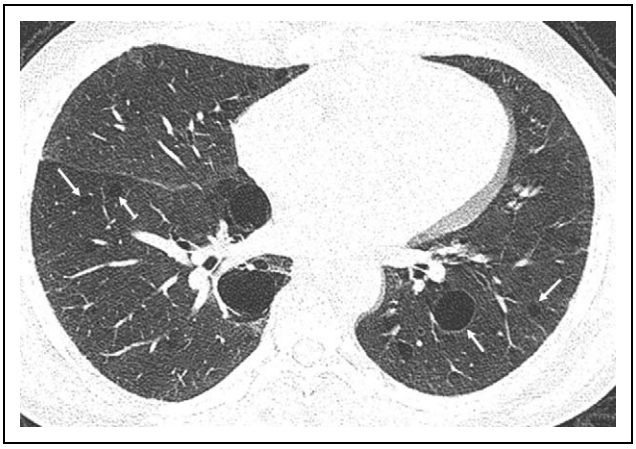

Figure 5. CT of a 51-year-old patient with Sjögren's syndrome showing scattered cysts of varying sizes (arrows) and the suggestion of a mild increase in background attenuation consistent with lymphocytic interstitial pneumonia.

Lung involvement

Lung involvement in SjS includes a wide spectrum of airway (both large and small airways involvement is common), interstitial and lymphoproliferative disorders. The frequency of abnormal findings varies widely depending on inclusion criteria, patient selection and method of ascertainment (whether by HRCT-imaging[144-148] or by functional tests[149-154]). However, when stringent criteria are applied, the prevalence of clinically significant lung involvement has been estimated at 11% in a recent large study of 1010 Spanish SjS patients.[155] Pleuritis,[156] pulmonary arterial hypertension,[157] middle lobe syndrome[158] and shrinking lung syndrome[159] have been reported in SjS, albeit rarely.

More than half of SjS patients report respiratory symptoms, including hoarseness (dry larynx), dry cough (xerotrachea),[149,151-153,160-162] and exertional breathlessness. A high frequency of respiratory-tract infections is also observed,[162] possibly secondary to reduced mucus secretion and lymphocytic infiltration of the small airways, leading to impaired microbial clearance.[163]

Interstitial lung disease

Clinically significant ILD occurs in a minority of patients, as SjS-associated ILD tends to be mild and self-limiting. However, limited disease is present in a substantial proportion of patients, as suggested by the finding of a restrictive pulmonary defect and/or a reduction in DLCO in as many as 17%–37.5% of SjS patients.[153,161,164]

Studies conducted after the ATS/ERS Consensus classification[8] suggest NSIP as the most frequent among histological patterns, although OP, LIP and UIP are also observed.[18,160,165,166] The discrepancy with previous studies reporting a high frequency of SjS-associated LIP may be secondary to the reclassification of LIP as cellular NSIP in some cases, while others previously classified as LIP would now be considered as low-grade lymphoma.[167]

Reported HRCT findings consistently include ground glass attenuation, reticular opacities and consolidation as the preponderant patterns,[18,116,160,166] while honeycombing occurs infrequently.[18,146,148,160] A CT pattern consistent with NSIP has been found to be highly correlated with a histological NSIP pattern, while CT findings other than NSIP have a poor predictive value.[160] CT features of LIP include ground glass abnormalities, reflecting the homogeneous lymphocytic infiltration; thin-walled perivascular cysts may also occur (Figure 5). Centrilobular and subpleural nodules are also observed frequently and are believed to reflect lymphocytic bronchiolitis. Unfortunately, a LIP pattern can be difficult to clearly distinguish from malignant lymphoma,[168] thus affecting surgical biopsy considerations. Amyloidosis, in which cystic lesions are found associated with nodules, often impinging on the cystic cavity,[116,147] is more frequently described in SjS than in other CTDs.[68,160]

ILD is not infrequently associated with airway abnormalities in SjS patients,[160,166] similarly to that seen in RA.[68,169] It follows that restrictive, obstructive or mixed patterns can all be found in SjS. On BAL, a subclinical lymphocytic and neutrophilic alveolitis is seen in up to 50% of SjS patients.[170,171] BAL neutrophilia, alone or combined with lymphocytosis, has been associated with functional progression of disease.[164,171] In the case of CT features clearly suggestive of NSIP, a surgical biopsy is not required, although it should be considered in non-NSIP CT cases, particularly if there are features suggestive of lymphoma, as mentioned below.[160,168]

Pulmonary lymphoma. SjS is associated with a 34- to 44-fold increase in malignant lymphoma.[172-175] Although pulmonary lymphoma occurs less frequently than lymphoma at other sites, such as the parotid gland,[156,175] it represents approximately 20% of SjS-associated lymphomas,[175-178] with reported prevalences ranging between 1% and 10% of SjS patients.[146,150,172,179] Honda and colleagues compared HRCT findings of LIP versus malignant lung lymphoma in 17 pSS patients against 44 patients with pulmonary lymphoma.[168] Although features of consolidation, large nodules (>10 mm) or pleural effusion were associated with lymphoma, the two conditions overlapped with regard to ground glass attenuation, small nodules and hilar-mediastinal lymphadenopathy.[168] By contrast, cysts were present in almost all patients with LIP (14/17, 82%) but only in one patient with malignant lymphoma.

Management. Overall, patients with SjS have a good prognosis.[149,179] Excess mortality has been related mainly to lymphoproliferative conditions.[179,180] Corticosteroids are largely used as first-line therapy[18,166] and may be the only agent required, particularly in LIP and OP patterns.[18,97] Other immunosuppressive agents including azathioprine, mycophenolate and cyclophosphamide can be used as corticosteroid sparing agents, and/or in case of continued progression with corticosteroids alone, although no clinically controlled trials exist to guide in treatment. Although ILD in the context of SjS usually stabilizes or improves on treatment, it can be associated with progressive worsening in a small minority of patients, particularly in patients with a UIP pattern.[18,150] Acute exacerbation leading to respiratory failure and death has been described, although rarely, in association with a UIP and NSIP pattern in the context of SjS.[18]

Table 7. Criteria for the diagnosis of systemic lupus erythematosus[184] Four criteria or more are required

Diagnostic criteria for SLE
Malar rash
Discoid rash
Photosensitivity skin rash
Oral or nasopharyngeal ulceration
Nonerosive arthritis involving two or more peripheral joints
Serositis (pleuritis, pericarditis)
Renal disorder (persistent proteinuria, cellular casts)
Neurologic disorder (unexplained seizures or psychosis)
Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia)
Immunologic disorder (positive LE cells, anti-DNA antibodies, anti-Sm antibodies, false-positive serologic test for syphilis)
Elevated antinuclear antibodies

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystem disease of unknown etiology, particularly affecting joints, skin, kidneys, serosa, vessels and the central nervous system. It is primarily seen in women in the reproductive years, with a prevalence varying from 164 per 100,000 (in Caucasians) to 406 per 100,000 (in African Americans).[181] Autoantibodies are a hallmark of SLE and virtually all patients have anti-nuclear antibodies (ANA). Disease-specific antibodies include anti-double stranded DNA and anti-Sm, found in 78% and 10% of patients with SLE, respectively.[182] Other SLE-associated antibodies, although not disease-specific, include anti-Ro/SSA and anti-La/SSB, found in 25% and 19% of patients respectively.[183] In view of the variability of presentation patterns, diagnostic criteria have been established. At least four of the updated diagnostic criteria are needed for a diagnosis of SLE (listed in Table 7).[184,185]

Respiratory manifestations are common, including pleural, parenchymal, respiratory muscle and pulmonary vascular involvement (Table 8). Although respiratory involvement is not included among the criteria, lung complications have a detrimental effect on prognosis.[186-189] Pulmonary involvement is common,[182,190-196] but respiratory symptoms are often absent or minimal.

Table 8. Respiratory manifestations of systemic lupus erythematosus

Respiratory manifestations	
Lung compartment	Disease
Lung parenchyma	Acute lupus pneumonitis; Interstitial lung disease
Pleura	Lupus pleuritis, with/without effusion
Airways	Laryngeal involvement; Bronchiectasis; Small airways disease
Vessels	Alveolar Haemorrhage; Pulmonary arterial hypertension; Antiphospholipid syndrome
Muscles	Shrinking lung syndrome
Other conditions: Infectious pneumonia, lung cancer	

Interstitial lung disease

Clinically significant ILD occurs in a minority of patients with SLE, with estimates ranging from 3% to 8%,[94,197-199] although trivial interstitial involvement is found in up to one third of lupus patients.[191,200,201] ILD may develop as a sequel to acute lupus pneumonitis/DAD pattern.[202] On CT, the most frequent abnormalities are interlobular (33%) and intralobular septal thickening (33%).[200] In view of the relative rarity of significant ILD, data on pathological patterns is limited. However, as with other CTDs, the most common pattern appears to be NSIP, although LIP, OP and UIP have also been observed.[68,116,191,200,203-205] In the absence of controlled clinical trials, the principles governing treatment of SLE-associated ILD are similar to the other CTDs.[206-208]

Life-threatening conditions

Acute lupus pneumonitis (ALP) is a poorly defined entity, estimated to occur in 1%–4% of patients with SLE, characterized by focal or diffuse pulmonary consolidation with an autoimmune rather than infectious origin. It is likely that the majority of cases represent diffuse alveolar damage (DAD) and/or diffuse alveolar haemorrhage. Clinically, the presentation is of acute onset dyspnoea, fever, cough and occasionally haemoptysis. Histological features are essentially those of diffuse alveolar damage, with alveolar edema, hyaline membranes and inflammatory cell infiltration. Capillaritis and alveolar haemorrhage are variably seen, as are deposits of immunoglobulins and complement.[192] On CT, bilateral ground glass opacities and/or consolidation are observed. Small bilateral pleural effusions are also common.[194] CT features are non-specific, and the differential diagnosis includes lung infection, pulmonary edema or a drug reaction. A BAL +/- transbronchial biopsy with a wide-ranging screen for infectious agents is recommended, if feasible. In view of the high frequency of infections in SLE and the difficulty in confidently excluding an infection in this scenario, broad-spectrum antibiotic therapy should be instituted early and maintained until infection is ruled out.

Diffuse alveolar haemorrhage (DAH) is a relatively rare condition, described in 1.5% of patients in a recently large published series.[209] It can be the presenting feature of SLE.[202,210,211] Similarly to acute lupus pneumonitis/DAD, DAH is characterized by an abrupt onset of breathlessness, fever and cough; half of patients report haemoptysis at presentation; a sudden drop in haemoglobin is highly suggestive.[192,194,202,212,213] Arterial hypoxemia is common and more than 50% of patients will need mechanical ventilation.

BAL is diagnostic, identifying increasingly bloody returns; on cytology, high numbers of red blood cells and haemosiderin-laden macrophages are seen. Chest HRCT appearances are comparable to acute lupus pneumonitis (bilateral consolidation and/or ground-glass opacities).[116,194] Histopathologically, features also overlap, although DAH includes findings of a neutrophilic capillaritis and extravasated red-cells filling the alveolar spaces.[192,194,212,213]

The prognosis of acute lupus pneumonitis and DAH is poor, with reported mortality rates of approximately 50% for both entities in historical series.[202,212,214] Survival may have improved in recent years, thanks to advances in ventilatory care and the prompt use of high dose corticosteroids and/or immunosuppressants, although this has not been formally evaluated. In view of the aggressiveness of these conditions, high-dose immunosuppressive treatment should be instituted promptly. Although no controlled studies are available, initial treatment usually includes high-dose intravenous methylprednisolone (1 g for 3 consecutive days), followed by oral corticosteroids, with the addition of intravenous cyclophosphamide in severe cases. Appropriate ventilatory supportive care is also crucial.[213-216] Plasmapheresis in DAH, with or without intravenous immunoglobulin in ALP, can be considered in case of failure of immunosuppressive

therapy.[192,202,211,217] The place of newer immunomudulatory agents still needs to be established, although rituximab has been used successfully in a case of lupus DAH unresponsive to conventional immunosuppression.[197]

Catastrophic antiphospholipid syndrome (APS) is a devastating condition that differs from classic APS for multiple and synchronous thrombotic events of small vessels, as opposed to single thrombotic events of medium-large ones.[218-220] The lung is affected in 2/3 of cases[221]; possible manifestations include diffuse alveolar damage, pulmonary embolism, pulmonary edema, alveolar hemorrhage and pulmonary artery thrombosis.[221,222] This syndrome bears a mortality rate of 50% despite aggressive treatment with anticoagulation, high dose corticosteroids, cyclophosphamide, plasmapheresis and intravenous gammaglobulins.[221-223]

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) can be due to SLE itself or can be an indirect consequence of SLE-associated manifestations, such as chronic thrombo-embolic disease (seen more frequently in anti-phospholipid syndrome) and, sporadically, fibrotic lung disease.[224] PAH has been variably reported in 4%–43% of SLE patients.[225-228] The management of SLE-associated PAH (not secondary to thromboembolic disease) includes the same classes of drugs used to treat idiopathic PAH (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and prostacyclin agonists). In addition, SLE-associated PAH can respond to immunosuppression, including intravenous methylprednisolone and/or intravenous cyclophosphamide therapy.[229,230] A recent survey showed a 3-year survival rate of 74% for SLE-associated PAH, significantly better than SSc-PAH, most likely because of its greater responsiveness to anti-inflammatory/immunosuppressive treatment (47%).[231] Of note, there has been one report of a patient with SLE-PAH successfully treated with rituximab.[232]

Undifferentiated CTD and overlap syndromes, including mixed connective tissue disease

In at least 25% of patients presenting with CTD-ILD, the signs and symptoms suggestive of a connective tissue disorder do not fit the criteria for any of the defined CTDs and may be classified as undifferentiated CTD (UCTD). Indeed, CTD features may be missed if not specifically looked for, suggesting that all patients with a diffuse lung disease benefit from a full autoimmune screen and detailed history for symptoms suggestive of a CTD. A large number of patients who would have previously been categorized as having idiopathic NSIP is likely to have underlying UCTD, although the relative proportions of idiopathic and UCTD-associated NSIP are likely to vary depending on the stringency of the UCTD criteria.[233] This may be particularly important in the context of a UIP pattern, as signs of a CTD such as Raynaud's phenomenon and the presence of autoimmune serology are likely to be associated with a significantly better survival than IPF, although this has not been formally evaluated.

Overlap features, in which serology and/or clinical manifestations of more than one CTD are present, are defined as overlap syndromes, the most studied of which is mixed connective tissue disease (MCTD). MCTD is characterized by features of lupus, systemic sclerosis and polymyositis and is serologically defined by the presence of anti-U1 RNP antibodies. Antibodies against other extractable nuclear antigens and high rheumatoid factor titers are also commonly found. Although the type and pattern of organ involvement is heterogenous, features which are commonly present in patients with MCTD include Raynaud's phenomenon, swollen fingers, presence of pulmonary hypertension disproportionate to the extent of interstitial involvement, more severe arthritis, and the absence of severe renal or central nervous system involvement. The lungs are very commonly involved in MCTD, with estimates of up to 67%,[234] although often lung disease is asymptomatic. The most common lung manifestations include pleural effusions, ILD with CT features (ground glass and reticulation) most frequently in keeping with an NSIP pattern, although honeycombing suggestive of a UIP pattern can also be seen, and pulmonary hypertension, which can be isolated or associated with ILD.[235,236]

Treatment of CTD-associated ILD; comparison with IPF

At least until single CTD-specific treatments for ILD are developed, and in the absence of controlled trials (except SSc-ILD), the treatment of CTD-associated ILD follows the same general principles regardless of the type of CTD. In contrast to IPF, it is only a subgroup of CTD patients in whom treatment should be considered. The decision to initiate treatment in CTD-ILD depends on severity of lung function abnormalities

and likelihood of ILD progression. Patients with only limited lung function impairment and/or CT extent of disease should probably be observed for a period of time to establish whether significant progression occurs before deciding on treatment.

In IPF, the benefit obtained from currently available treatment options remains uncertain, with no drug proven to improve survival, despite a number of recently completed randomized controlled trials.[237-239] Therefore, recruitment of IPF patients into high quality clinical trials remains a priority. When this is not possible, the available treatment for which there is some evidence of benefit is triple therapy with prednisolone (tapering over three months from an initial dose of 0.5 mg/kg to a maintenance dose of 10 mg once daily), azathioprine (2 mg/kg) and the anti-oxidant *N*-acetylcysteine (600 mg tds). This is based on the results of the IFIGENIA trial characterized by a better preservation of lung function in the group treated with azathioprine, prednisolone and *N*-acetylcysteine compared to prednisolone and azathioprine alone.[240] However, it is unclear whether *N*-acetylcysteine on its own has similar effects, and further trials addressing this are urgently required. Pirfenidone, an anti-fibrotic agent, is the other drug for which recent randomized placebo controlled trials have reached their primary end point (change in FVC at 1 year) in most, but not all, trials. Of the three recently completed phase III trials (two of which were reported at international meetings but have not yet been published),[241] two reached the primary endpoint of change in FVC at 1 year, whereas a non-significant trend in the same direction was reported for the other. Based on these results, pirfenidone has recently been licensed for use in IPF patients in Japan, but not in the United States or in Europe, at least for the moment. In conclusion, as stated in recent guidelines, no definitive treatment recommendations can be provided for IPF patients, and treatment with prednisolone, azathioprine and *N*-acetylcysteine only carries a weakly positive recommendation.[167] Supportive care (including palliative oxygen, pulmonary rehabilitation, opiates, treatment of gastro-oesophageal reflux) tailored to and carefully discussed with the individual patient is an integral part of the treatment strategy.[167] Enrolment in clinical trials, and early referral for lung transplant, if appropriate, are recommended.[167]

In contrast with IPF, CTD-ILD is often characterized by a clearer response to immunosuppression, in line with postulated autoimmune/inflammatory mechanisms playing a more significant role in CTD-ILD pathogenesis. As mentioned in the individual sections, response to treatment is often seen as stabilization in the face of previous progression, rather than improvement, particularly in the setting of a UIP or fibrotic NSIP pattern, although patterns in which inflammation plays a major role, such as OP, can improve dramatically on treatment. Based on the greater degree of response to immunosuppression, pulsed intravenous methylprednisolone and/or intravenous cyclophosphamide have a recognized place in the treatment of aggressive CTD-ILDs, whereas they have not been shown to be of benefit in IPF.[242,243]

In the presence of significant ILD, treatment options include corticosteroids, starting with a dose of 0.5-1 mg/kg in all CTD except for SSc (risk of renal crisis), often in combination with an oral immunosuppressant from the start. Azathioprine is the most commonly used oral immunosuppressant in CTD-ILD, although mycophenolate may be better tolerated; their comparative effectiveness has not been established. Azathioprine is usually started at a test dose of 50 mg once daily for a month, with weekly blood tests to assess full blood counts, liver and renal function tests; if this dose is well tolerated, the dose is increased to 150 mg once daily (or the equivalent 2 mg/kg, but not more than 200 mg daily), with continued blood tests performed at six weekly intervals thereafter. Mycophenolate is usually started at 250 mg bd, with increases of 500 mg at 2 to 4 weekly intervals until the full dose is reached, usually 1 g bd. Again blood tests are performed at 1–2 weekly intervals until the full dose is reached, and then repeated at 6–8 weekly intervals thereafter. Over time, if the disease stabilizes or responds to treatment, prednisolone is gradually tapered over the space of 6−12 months down to a maintenance dose of 10 mg once daily.

In the case of severe, and/or rapidly progressive ILD, it is crucial to rapidly gain control of the disease with high-dose corticosteroids (usually intravenous methylprednisolone) +/- intravenous cyclophosphamide. This is particularly true for those ILD patterns characterized by a high likelihood of progression and significant mortality (OP/DAD overlap [Figure 3]). Intravenous cyclophosphamide is usually substituted with an oral immunosuppressant such as mycophenolate or azathioprine after 6 months of treatment, if functional stability is obtained. In life-threatening disease and/or in disease that is continuing to progress despite aggressive immunosuppression, rituximab can be considered as salvage therapy and has shown

promising results in a few published case series and in the authors' experience. In a small retrospective case series of patients with Jo1+ polymyositis,[135] rituximab led to a reversal of ongoing progression occurring despite traditional immunosuppression in 7 out of 11 patients. A small prospective study has assessed the efficacy of rituximab in SSc-ILD, although in this case patients had stable disease.[244] Although not supported by formal studies, the most frequently used dosing regimen is rituximab 1 g, followed by a further 1 g after 2 weeks. No information is available on longer term use of rituximab, and the frequency of subsequent doses, if needed. Although a controlled clinical trial in the context of salvage therapy in a life-threatening scenario is not feasible, clinical trials of rituximab for use in severe disease in CTD-associated ILD are needed, to establish the patterns and CTDs in which it is likely to be of benefit.

Studies evaluating the optimal duration of immunosuppressive treatment in the different CTD-ILDs are lacking. However, if the disease was considered sufficiently severe and/or progressive to initiate immunosuppressive treatment, we would recommend that in most cases this should be maintained at a stable dose for at least the following 2−3 years, particularly in patients with a short history of CTD, as the early years are likely to be the most strongly associated with active disease. Immunosuppressive treatment should in any case be reduced gradually, with frequent lung function monitoring to ensure ongoing stability, particularly after having stopped treatment altogether. The willingness to stop treatment will naturally be higher in less severe disease and/or in disease that has shown dramatic responses to oral corticosteroids, as further relapses are likely to be more responsive to future courses of treatment.

In view of the frequently seen stabilization of CTD-ILD progression on immunosuppressive treatment, considerations regarding timing of referral to transplant also differ markedly between CTD-ILD and IPF. In IPF, in view of the dismal prognosis and relative lack of response to available treatments, referral for lung transplant is suggested when the disease is extensive (DLCO <40%) and/or progressive (>10% decline in FVC and/or >15% decline in DLCO).[167] In CTD-ILD, it is only patients with extensive disease who continue to decline despite maximal immunosuppression, for whom lung transplant should be considered. Concomitant significant gastro-oesophageal reflux and/or extrapulmonary involvement (for example severe muscle disease in PM/DM) represent relative contraindications which need to be discussed on a case by case basis with the transplant centre.

In conclusion, treatment should be started early in CTD patients whose lung disease is likely to progress if left untreated. At the moment, the main markers of likelihood of ILD progression are disease severity, evidence of recent functional decline, and short duration of systemic disease. However, research is needed to identify non invasive prognostic biomarkers of likelihood of disease progression, so that treatment can be started before any irreversible damage to the lungs occurs. Unless reversible disease such as OP is identified on CT, the main aim of treatment is to prevent further progression, and stabilization in the face of previous deterioration should be viewed as a success. Controlled therapeutic trials are needed to establish the least toxic and most effective long term immunosuppressive treatment for CTD- associated lung disease.

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