Multidisciplinary Evaluation in Patients with Lung Disease Associated with Connective Tissue Disease

Athol U. Wells, MD1 Ananad Devaraj, MD2 Elizabetta A. Renzoni, MD, PhD1 Christopher P. Denton, MD3

1 Interstitial Lung Disease Unit, Department of Imaging, Royal Brompton Hospital, London, United Kingdom

2 Department of Imaging, Royal Brompton Hospital, London, United

Kingdom

3 Department of Rheumatology, Royal Free Hospital, London, United Kingdom

Semin Respir Crit Care Med 2019;40:1–10.

Address for correspondence Athol U. Wells, MD, Q4Interstitial Lung

Disease Unit, Royal Brompton Hospital, Sydney ST, Chelsea, London

SW3 6HP, United Kingdom (e-mail: Athol.Wells@rbht.nhs.uk).

Abstract Multidisciplinary diagnosis is now viewed as the diagnostic reference standard in interstitial lung disease (ILD). This process consists of the integration of the evidence base with clinical reasoning in the formulation of a diagnosis and requires input from clinicians, radiologists, and, in selected cases, histopathologists. In ILD associated with connective tissue disease (CTD-ILD), multidisciplinary evaluation is especially helpful when CTD is suspected but cannot be diagnosed using strict criteria. In this context, the integration of systemic clinical data, serologic information, and computed tomography and biopsy findings may allow CTD-ILD to be diagnosed. However, the value of multidisciplinary evaluation in CTD-ILD is not confined to diagnosis. The frequent coexistence of pulmonary processes other than ILD, including pulmonary vascular

> diagnosis

> disease severity

> prognostic evaluation

> disease progression

disease, extrapulmonic restriction, and airways disease, often has a major impact on symptoms and pulmonary function tests (PFTs). In this review, we highlight the value of multidisciplinary discussion (MDD) in reconciling clinical data, PFT, and imaging data in the accurate staging of disease severity, baseline prognostic evaluation, and the identification of progression of ILD. MDD also provides a means to combine the views of respiratory physicians and rheumatologists in formulating a treatment strategy. It is often possible to reach a robust view as to whether management should be driven by systemic disease, pulmonary disease, or both. When treatment needs to be introduced or modified for both systemic and pulmonary reasons, face-to-face discussion facilities the selection of therapeutic agents that are likely to be efficacious for both systemic and pulmonary diseases.

Multidisciplinary discussion (MDD), integrating and recon- ciling clinical, radiographic and histopathologic data, is now the diagnostic reference standard in interstitial lung disease (ILD).1 The need for MDD is viewed as axiomatic in the diagnosis of most of the more prevalent ILDs, including idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), and hypersensitivity pneumonitis. However, MDD has not traditionally been required in the diagnosis of ILD associated with connective tissue disease (CTD-ILD) as the diagnosis merely requires the presence of ILD as judged by computed tomography (CT) and confirmation of a systemic disorder. In general, in CTD- ILD, identification of the underlying histologic pattern (usually NSIP, with or without an element of organizing pneumonia [NSIP/OP overlap], or usual interstitial pneumo- nia [UIP]) is not helpful in prognostic evaluation.2 The exception is ILD associated with rheumatoid arthritis (RA-ILD), in which the distinction between UIP and NSIP, whether based on biopsy or HRCT findings, is a strong determinant of outcome3–9: in RA-ILD, this distinction merits MDD, as in idiopathic disease. However, current data indicate that the underlying histopathologic pattern has little impact on out- come in ILD associated with systemic sclerosis (SSc-ILD) or inflammatory myopathy (IM-ILD), and a histologic pattern of UIP is, moreover, rarely associated with either systemic disorder3,10 or with Sjogren's syndrome.11 This may apply equally to ILD associated with systemic lupus erythematosus (SLE-ILD), based on accumulated clinical experience, but data are sparse due to the low prevalence of chronic ILD in SLE.

However, although diagnostic MDD may not seem to be pivotal, CTD-ILD poses unique problems which can only be resolved by MDD, due to the multiplicity of cardiorespiratory problems that may coexist with ILD. An understanding of the severity of ILD in an individual patient requires the con- founding functional effects of other disease processes to be taken into account, with the integration of pulmonary func- tion tests (PFT) with clinical, CT, and echocardiographic data. Exactly the same integrative process is needed in the decon- struction of change in disease severity: has ILD progressed or is symptomatic change due to change in a concurrent disease process or the development of opportunistic infection?

Thus, the disciplines that need to be integrated in the evaluation of CTD-ILD differ from the usual triad of clinical, radiologic, and histopathologic data that are reconciled in the traditional multidisciplinary diagnosis of other ILDs. Rheumatologist participation is also invaluable, both in diagnostic evaluation (when CTD is suspected but not cer- tain, as in the entity of "interstitial pneumonitis with auto- immune features" [IPAF]), and in the formulation of treatment goals, that is, the determination of whether ther- apeutic intervention should be driven by systemic disease, pulmonary disease, or both.

In this review, we discuss the particular difficulties of diagnosis, ILD severity staging, the identification of serial change in ILD severity, and the formulation of treatment goals in CTD-ILD. Although none of the problems has fallen within the scope of traditional MDD in ILD, we share a growing consensus that their complexity amply justifies routine MDD, with participation by respiratory physicians, rheumatologists, and thoracic radiologists, and ready access to expertise in pulmonary vascular disease.

The Broad Applicability of MDD in the Evaluation of ILD

Although the perceived role of MDD in ILD has been confined to diagnosis, other difficult issues are routinely discussed in multidisciplinary meetings. It should be emphasized at the outset that the diagnosis reference standard status of MDD has never been validated, simply because any candidate reference standard is incorporated within a MDD.1 In prin- ciple, diagnoses made by MDD might ultimately be validated against outcome12: in this regard, there is support from the observation that the distinction between IPF and other ILDs has a greater prognostic value when made by MDD than when made in isolation by clinicians, CT radiologists, or histopathologists.13 As discussed later, diagnostic MDD is relevant to patients with possible CTD, not satisfying classi- cal CTD diagnostic criteria. However, the wider value of MDD relates to uncertainties that are highly prevalent in CTD-ILD: difficulties in assessing severity, serial change, and the designation of appropriate treatment priorities, due to the multiplicity of cardiopulmonary disorders coexisting with CTD-ILD.

The process of MDD consists of amalgamating skills in separate domains, reconciling diverse perceptions, and negotiating a consensus view. Prior to MDD, it was necessary for individual clinicians to integrate reports made by CT radiologists and histopathologists, often without detailed discussion of the certainty of observations and the sustain- ability of differential diagnoses. The interpretation of PFT in complex cases is not a ubiquitous clinical skill but is facili- tated by the integration of PFT with CT observations in MDD. The impact of MDD on management decisions, balancing systemic and pulmonary imperatives, is another area in which face-to-face negotiation with a participating rheuma- tologist has major advantages.

The advantages of MDD are threefold. First, participants must present their views to skilled colleagues in a setting in which their observations can be challenged and, in some cases, be seen to be imprecise. Peer review is generally viewed as a powerful tool to improve the quality of medical care. This is a process in which the logic of conclusions reached by clinical reasoning can be questioned and debated by trained observers, independently of the particular spe- cialist skills of participants. Second, MDD allows the cer- tainty of observations within individual domains to be carefully weighted with emphasis given to observations made with greater confidence in the formulation of a con- sensus view. Finally, a group view adds confidence to clin- icians and patients in cases in which diagnosis, severity staging, and the identification of progression or manage- ment decisions are a very close call.

Diagnosis of CTD-ILD: The Role of MDD

As discussed earlier, MDD is not required in the diagnosis of CTD-ILD when a CTD is definitely present, as judged by classical diagnostic criteria. However, there is a large sub- group of patients with suspected CTD, based on suggestive clinical and serologic data, without the satisfaction of

formal CTD diagnostic criteria. The entity of IPAF, reviewed in detail elsewhere in this issue, was constructed by an expert group14 in order to standardize "lung-dominant CTD" and explored historically in series with differing definitional criteria. IPAF has yet to be endorsed as a true diagnostic entity: the purpose of the American Thoracic Society/European Respira- tory Society IPAF statement was to facilitate research in this field, with the intention that the definition of IPAF definition ultimately be refined.14 With this caveat, the criteria used to define IPAF can be viewed as providing useful guidance as to the likely presence of an autoimmune diathesis. As discussed in detail elsewhere in this issue, IPAF criteria are met with satisfaction of two of three domains (clinical, serologic, and morphologic). However, there are major uncertainties with the rigid application of both the clinical and morphologic criteria, when it comes to the judgment that an individual patient has a diagnosis of CTD-ILD.

With regard to the clinical domain, some CTD manifestations, excluded because of their nonspecific nature, would sometimes be viewed as highly relevant on rheumatologist evaluation of individual patients. For example, mild sicca symptoms are an unreliable guide as to the presence of a Sjogren's element, but this does not apply to severe symptoms leading, for example, to oral or ocular ulceration. Furthermore, temporal clustering of various manifestations of disease is not included in the IPAF definition. When lung disease develops concurrently with sicca symptoms, the new onset of severe gastroesophageal regurgitation and arthralgia (without a definite inflammatory arthropathy), the thinking clinician is likely to stronglyQ6 suspect that these features are linked as part of a CTD, even though formal clinical criteria for IPAF are not satisfied.15 This perception can be integrated into the formulation of a multidisciplinary diagnosis of CTD-ILD.

The morphologic domain also poses problems. Multi- disciplinary evaluation is often needed to determine whether CT features are genuine to those of NSIP. This applies especially to patients with suspected CTD-ILD and CT appearances of "probable UIP," as defined in the Fleischner Society white paper on IPF diagnosis.1 While UIP may be highly probable in elderly patients with idiopathic disease, presenting with this CT pattern, fibrotic NSIP is more likely to be the underlying histologic pattern in younger patients with known or suspected CTD. The difficulties faced by histo- pathologists and radiologists working in isolation are high- lighted by observations in a study of ILD multidisciplinary practice, with the same data presented to seven expert groups. There was very poor agreement between CT radi- ologists and between pathologists on the presence of fea-

tures suggestive of CTD on CT and biopsy, respectively.13 The identification of multicompartment disease is an often nebulous area. In a large pivotal IPAF clinical series,16 the IPAF morphologic criterion was considered to be met if there was elevation of the forced vital capacity (FVC)/diffusing capacity for carbon monoxide (DLCO) ratio above a designated threshold, indicating the presence of pulmonary vasculopathy. However, pulmonary vascular limitation, with or without fixed pulmonary hypertension, an expected complication of advanced ILD, typically results in the elevation of the FVC/DLCO ratio. The judgment that pulmonary vascular limitation is "disproportionate" to ILD (a requirement explicitly specified in the IPAF statement14) cannot be based on an agreed definition of disproportionate vasculo- pathy as no such definition exists. MDD is required in order to reach the conclusion that pulmonary vascular disease is present and out of keeping with ILD severity. Similarly, MDD is often required to reach the conclusion that there is unexplained airflow obstruction compatible with IPAF in current or former smokers: airway disease may represent a CTD manifestation but may equally reflect smoking-related damage, with the distinction often based on an evidence that airflow obstruction has or has not developed following smoking cessation, or by the conclusion that the severity of airflow obstruction is out of keeping with CT evidence of smoking-related lung damage.

It might be argued that rheumatologist evaluation would provide the flexible assessment that is needed to conclude that a CTD is likely to be present in patients not satisfying classical CTD diagnostic criteria, with this information integrated into diagnosis without the need for MDD. However, as this judg- ment is often marginal, and conclusions reached on the satisfaction of morphologic criteria are often equally marginal, there is a compelling view that MDD, reconciling these uncer- tainties, is highly desirable, with input from expert ILD phy- sicians, CT radiologists, and rheumatologists, if a plausible working diagnosis of CTD-ILD is to be made. In IPAF, satisfac- tion of domain criteria often requires access to both rheuma- tologic and CT expertise: it is appropriate that in marginal cases, both skills should be represented in face-to-face discus- sion. In many cases, the diagnosis of CTD-ILD has a similar level of uncertainty to the uncertainty often present in the formula- tion of a diagnosis of chronic hypersensitivity pneumonitis, in which MDD is widely considered to be essential.

Staging of ILD Severity in CTD-ILD

In most ILDs, disease severity can be staged using character- istic PFT profiles. A glossary of PFT abbreviations is shown in ►Table 1. PFT are considered to be superior to symptoms

Table 1 Glossary of abbreviations used for measures of pulmonary function variables

FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
FEV1/FVC	Ratio of FEV1 to FVC, calculated using absolute values (L)
VA	Alveolar volume
DLCO	Carbon monoxide diffusing capacity
KCO	Carbon monoxide transfer coefficient
FVC/DLCO	Ratio of FVC to DLCO, calculated using percentage predicted values

in this regard and this applies especially to CTD-ILD, in which systemic disease may result in major exercise intolerance due to the increased work of locomotion. Equally, severe disability due to major musculoskeletal limitation may mask ILD-related exertional breathlessness. In individual patients, evaluation of disease extent on CT is sometimes helpful but unlike PFT, CT scoring requires subjective estimation and does not produce standardized data that are easily acquired in routine practice. In IPF, idiopathic NSIP, and chronic hypersensitivity pneumonitis, FVC and DLCO levels are used to stage severity, with threshold values of both measures used as severity exclusion criteria in

pivotal IPF treat- ment trials.17,18 In MDD of these disorders, disease severity is readily communicated by these variables, along with arterial gases in advanced disease.

However, in CTD-ILD, severity staging is much less straightforward because of the frequent existence of signifi- cant concurrent disease processes. Any of the number of disorders may be the dominant process responsible for respiratory symptoms but in many cases, two or more disease processes make a major contribution to exercise intolerance, confounding the assessment of ILD severity. The complex interaction between ILD, pulmonary vasculo- pathy, and other complications can only be deconstructed by reconciling PFT with clinical features and the extent of disease as judged by CT.

The considerable variability in patterns of PFT impair- ment in CTD-ILD reflects variable contributions from ILD (usually pulmonary fibrosis or OP), pulmonary vascular limitation (ablative vasculopathy, pulmonary thromboem- bolism, vasculitis), extrapulmonic restriction (pleural dis- ease, respiratory muscle weakness, diffuse cutaneous SSc), intrinsic airway disease (bronchiectasis, various forms of bronchiolitis), and centrilobular emphysema more often in smokers but also seen in nonsmokers. The relative preva- lence of concurrent pulmonary disease processes in indivi- dual CTDs is shown in ►Table 2. PFT may also be impaired due to heart failure (due to cardiomyopathy in SSc and IM), drug-induced lung disease, lower respiratory tract infection (reflecting immunosuppression), and the anemia of chronic systemic disease (leading to reduced measures of uncor- rected gas transfer).

Patterns of PFT impairment in individual pulmonary disorders complicating CTD (►Table 3) do not differ from those in idiopathic disease. As in other forms of ILD,19 CTD- ILD is characterized by a restrictive ventilatory defect (reduced FVC, increased forced expiratory volume in 1 second [FEV1]/FVC ratio, associated with a reduction in DLCO, which usually exceeds the reduction in FVC). Arterial oxygen levels are usually well preserved in isolated CTD-ILD until disease is advanced, and more so than in IPF of comparable severity.20

However, in OP, disproportionate hypoxia is frequent due to shunting of blood through consolidated lung.21 Pulmonary vascular disease in both CTD-ILD and idio- pathic vasculopathy is associated with a disproportionate fall in DLCO, quantified as a reduction in carbon monoxide

transfer coefficient (KCO) (a measure of blood volume per unit volume of ventilated lung).22 Importantly, major reductions in DLCO and KCO levels due to pulmonary vasculopathy may occur in the absence of pulmonary hypertension, due to the large pulmonary vascular reserve. Pulmonary hypertension should be suspected when severe resting hypoxia or major exertional oxygen desaturation is associated with a disproportionate reduction in gas transfer (severe hypoxia due to ILD complicates CTD-ILD only when disease is very advanced, unlike IPF20).

KCO levels have a significant advantage over the FVC/DLCO ratio as a measure of disproportionate reduction in DLCO, due to much lower measurement variability. DLCO is calcu- lated as a composite of measured KCO and measured alveolar volume (VA) with the greater variability of DLCO measure- ment (compared with lung volumes) reflected variability in both components, especially VA. Thus, KCO estimation is associated with the measurement variation of a single vari- able, whereas the FVC/DLCO ratio is confounded by the measurement variability of KCO, VA, and FVC. This may explain the fact that in the evaluation of the prognostic significance of PFT trends in a large SSc-ILD cohort, a 10% serial reduction in KCO was associated with increased mor- tality, but a 20% rise in the FVC/DLCO ratio was required for

Table 2 Semiquantitative estimation of the relative prevalence of functionally significant pulmonary disease processes in CTD, applicable equally to CTD-ILD

Table 3 Patterns of PFT impairment in the more frequent pulmonary complications of CTD

	Pattern of ventilatory impairment	Carbon-monoxide dif- fusing capacity (DLco)	Arterial gases at rest
Interstitial lung disease	Restrictive ventilatory defect	Reduced, with values usually lower than volumes but KCO levels normal or mildly reduced	Resting hypoxia in end- stage disease
Pulmonary vascular disease	Normal	Reduced, with both DLCO and KCO severely reduced in pulmonary hypertension	Resting hypoxia in pul- monary hypertension but not in less severe vasculopathy
Bronchiectasis	Obstructive or mixed ventilatory defect	Highly variable	Resting hypoxia in end-stage disease
Extrapulmonary restriction	Restrictive defect. Reduction in peak flow may indicate muscle weakness	DLCO levels low, nor- mal, or mildly reduced. KCO levels supranormal.	In severe disease, hypercapnic respiratory failure, normal alveolar–arterial oxygen gradient

Abbreviations: CTD connective tissue disease; DLCO, carbon monoxide diffusing capacity; KCO, carbon monoxide transfer coefficient; PFT, pulmonary function tests.

the same prognostic discrimination.23 The focus on the FVC/ DLCO ratio in recent decades24,25 is likely to reflect the fact that in many PFT laboratories, KCO and VA values are not provided, even though both must be measured in order to

compute DLCO levels. This caveat aside, KCO levels and the FVC/DLCO ratio provide broadly equivalent information in the PFT evaluation of the pulmonary vasculature.

In significant pleural disease, there is a restrictive ventilatory defect,26 exactly as in CTD-ILD. However, reductions in DLCO levels tend to be minor and KCO levels typically rise to supranormal values27 (as the total pulmonary blood volume changes little, even with major reductions in lung volumes). PFT impairment in respiratory muscle weakness is similar to that in other extrapulmonic restrictive processes. However, severe muscle weakness is often associated with an effect on the effort-dependent early part of the expiratory flow- volume curve, with disproportionate reductions in peak flow.28 Importantly, PFT are insensitive except in severe

muscle weakness, with a reduction in muscle strength of at least 50% required before lung volumes are reduced.29 In severe extrapulmonary restriction, alveolar hypoventilation may manifest as hypoxia, hypercapnia, and a normal calculated alveolar–arterial oxygen gradient, a profile seen most often in respiratory muscle weakness.30

Both smoking-related emphysema and intrinsic airway disease (forms of bronchiolitis) are characterized by an obstructive ventilatory defect. DLCO and KCO levels are strikingly reduced in emphysema,31 but typically remain

normal in isolated intrinsic airways disease, unless the FEV1 falls below 1 L.32 KCO levels are preserved, even in advanced bronchiolar disorders, in the absence of pulmonary hyper

tension. Thus, in MDD, in patients with little or no emphy- sema and limited CTD-ILD on CT, the combination of severe airflow obstruction and preservation of measures of gas transfer strongly suggests that symptoms, if present, are due to a bronchiolitic disorder (in the absence of bronchiec- tasis and asthma).

Rationalizing Patterns of Functional Impairment in MDD

Knowledge of classical patterns of PFT impairment, described earlier, is required in order to rationalize PFTs when pathological processes coexist in CTD-ILD. In that setting, PFT patterns are no longer typical of individual disease processes but can be deconstructed in MDD. Characteristic PFT profiles when CTD-ILD is associated with another pulmonary complication are shown in ►Table 3.

Knowledge of the functional effects of coexisting pro- cesses applies particularly to isolated or disproportionate reductions in DLCO, which may reflect the presence of pulmonary vasculopathy, the coexistence of pulmonary fibrosis and emphysema, or the combination of all three disease processes. Combined pulmonary fibrosis and emphysema (CPFE) in IPF results in the relative preservation of lung volumes, which may be normal, even when both processes are extensive on CT, and severe reductions in DLCO and KCO levels.33 The importance of CPFE in CTD-

ILD has only recently been appreciated. In a large cohort of SSc-ILD patients, CPFE was present in 15% of current or former smokers and 7.5% of life-long nonsmokers.34 Even more strikingly, In RA-ILD, CPFE has been reported in 27% of nonsmokers.35 In both cohorts, a subset of patients had typical CPFE PFT profiles, although this effect was less on average than in CPFE in idiopathic ILD, with emphysema often limited in extent in CTD-ILD. Thus, spirometric volumes in isolation are often misleading when the severity of ILD is staged in patients with concurrent emphysema, underlining the importance of integrating CT observations.

Table 4 Typical patterns of PFT impairment in the more frequently combinations of CTD-ILD and other pulmonary complications

Pulmonary fibrosis Centrilobular emphysema Lung volumes mildly impaired (restrictive or obstructive) or paradoxically normal. Dispro- portionate/severe reduction in DLCO, KCO. Disproportionate hypoxia at rest or on exercise often present

Pulmonary fibrosis Pulmonary hypertension Restrictive lung volumes. Disproportionate/severe reduction in DLCO, KCO. Disproportionate hypoxia at rest or on exercise often present

Pulmonary fibrosis Extrapulmonary restriction Restrictive, often severe ventilatory defect. DLCO less severely impaired than expected, KCO high, normal, or increased. Hypoxia at rest or on exercise frequent: alveolar–arterial oxygen gradient highly variable

Abbreviations: CTD connective tissue disease; DLCO, carbon monoxide diffusing capacity; ILD, interstitial lung disease; KCO, carbon monoxide transfer coefficient; PFT, pulmonary function tests.

The identification of pulmonary vascular disease in CTD- ILD also causes difficulties, especially when it contributes to major reductions in pulmonary reserve but is not sufficiently severe to manifest as pulmonary hypertension. As in idio- pathic pulmonary vascular disease, discussed earlier, dis- proportionate reductions in DLCO, quantified by KCO levels or elevations in the FVC/DLCO ratio,

often prompt further investigation, although the absence of pulmonary hyperten- sion does not exclude clinically significant pulmonary vas- culopathy. It should be stressed that major reductions in DLCO that are disproportionate to lung volumes exist equally in pulmonary hypertension secondary to CTD-ILD and "dis- proportionate" pulmonary hypertension out of keeping with CTD-ILD severity. This judgment is best made in MDD, with the integration of symptoms, PFT, and crucially, skilled interpretation of the extent of disease on CT, often a difficult call when interstitial abnormalities are subtle but widespread

An additional problem, in reconciling disease extent on CT with FVC levels, is that in some CTD-ILD cases, there are major selective reductions in lower lobe volumes due to pulmonary fibrosis (due to the predominant lower lobe distribution of UIP and NSIP). The phenomenon of apparently limited ILD on subjective CT evaluation in association with extreme reduction in lower lobe volumes has recently been described in an IPF cohort, in which global CT extent and the degree of retraction of the major fissure below its normal anatomical site (the top of the diaphragm, ►Fig. 1) were equally powerful determinants of reduction in FVC levels.36 At our institution, we have observed that this CT sign is frequently a key component of reconciling discrepancies between the CT extent of CTD-ILD and PFTs, especially in SSc-ILD and IM-ILD.

Careful multidisciplinary evaluation is even more valu- able when pulmonary hypertension is suspected in CTD-ILD patients with CPFE. A judgment must be made whether the extent of emphysema on CT is sufficient to account for disproportionate DLCO reduction. Furthermore, enlarge- ment of the pulmonary artery on CT or an increase in the ratio of the diameters of pulmonary artery/aorta are helpful ancillary signs increasing the likelihood of pulmonary hyper- tension associated with ILD.37,38 These signs, along with echocardiography, severe exercise desaturation39,40 and ele- vations of serum brain natriuretic peptide levels41 provide a

basis for the selection of patients to undergo right heart catheterization. However, this decision is a close call and, in principle, is more likely to be accurate if CT observations, clinical and PFT findings, and other tests are integrated in MDD.

Multidisciplinary Prognostic Evaluation

The prognostic value of baseline PFT in patients with CTD- ILD has been most frequently studied in SSc-ILD with increas- ing impairment of all resting PFT and exercise variables associated with increased mortality.42 However, these observations do not provide clinicians with a clear separation between low- and high-risk patient subgroups as outcomes have generally been examined against PFT analyzed as continuous variables, with occasional exceptions. In IM-ILD, DLCO levels <45% of predicted are associated with a substantial increase in mortality.43 In a large placebo-controlled trial of cyclophosphamide, serial FVC decline in the placebo arm was largely confined to patients with FVC levels <70% of predicted.44 The GAPQ10 staging system, based on designated FVC and DLCO thresholds and first explored in IPF,45 has provided significant separations in mortality between CTD-ILD subgroups.46

However, although these data provide information on average cohort effects, their use in isolation in individual patients is problematic for two reasons. The confounding effect of the normal premorbid pulmonary function range cannot be taken into account. For example, an FVC threshold of 70% presupposes a loss of FVC of 30%. However, in patients with premorbid values of 80% of predicted, there is a loss of FVC of only 13% from baseline. By contrast, when premorbid values approach 120% of predicted, an FVC level of 70% represents a reduction of more than 40% from baseline. Equally, it

cannot be supposed that designated thresholds are especially helpful when individual patient values lie close to a threshold. Is it plausible, for example, with regard to the DLCO threshold suggested in IM-ILD,43 that a patient with a DLCO level of 44% is likely to have a worse outcome than a patient with a DLCO level of 46%? The prognostic value of specific thresholds is likely to

be driven by those patients with PFT values that lie either substantially above or below the designated threshold value. Formal CT scoring of the extent of disease, as a means of defining high- and low-risk patient groups, is equally flawed. While there is no confounding effect from a normal pre- morbid range, the process of CT scoring is arduous and in any case, the limited value of thresholds in patients with PFT levels close to a threshold applies equally to CT estimation of disease extent. A threshold CT extent score of 20% provided prognostically powerful separations in a large SSc-ILD cohort,47 but this required intense evaluation by skilled CT observers, with significant observer variation as to whether individual patients were scored as above or below the 20% threshold value.

Multidisciplinary evaluation provides an elegant solution. In the study cited earlier, PFT and CT evaluation were combined.47 A rapid judgment was possible in more than two-thirds of SSc- ILD patients that CT extent was either substantially lower or higher than 20% of the lung. In one-third of cases with disease extent on CT close to 20%, an FVC threshold of 70% was used to adjudicate whether lung disease was limited or extensive. The prognostic value of this system in SSc-ILD, reproduced in subsequent studies,48,49 was substantially higher than distinctions made using either CT or PFT in isolation.47 In a recent report of a large RA-ILD cohort, distinctions made using this combined CT/PFT staging system resulted in striking prognostic separations, significantly more powerful than those pro- vided by CT distinctions between UIP and non-UIP.50 However, although CT evaluation is rapid, it requires expertise, taking into account major reductions in lower lobe volumes when the extent of fibrosis is apparently but misleadingly limited. MDD in individual patients results in careful scrutiny of CT findings with exploration of alternative causes of FVC reduction (i.e., forms of extrapulmonic restriction) when there is major dis- cordance between FVC values and CT appearances. In this way, MDD usefully refines prognostic evaluation based on the severity of CTD-ILD.

Multidisciplinary Evaluation of CTD-ILD Progression

As in idiopathic ILD, the identification of disease progression in CTD-ILD is based on the integration of symptomatic change, pulmonary function trends, and, in selected patients, serial CT evaluation. However, when evaluated in isolation, each monitoring domain has major limitations which pose particular difficulties in CTD-ILD.

In CTD-ILD, increasing exercise intolerance is not a reli- able guide to ILD progression. Coexistent arthropathy or myopathy is an important confounding factor, with flares in systemic disease leading to exertional dyspnea due to the increased work of locomotion. Furthermore, reduced physi- cal activity due to systemic disease may lead to loss of exercise tolerance due to weight gain or loss of fitness. Exertional dyspnea may also be aggravated by the coexistent pulmonary vascular, extrapulmonic restrictive, and airway complications of CTD, discussed earlier, and also by cardiovascular disease, which is increased in prevalence in patients with CTD-ILD.51 Thus, worsening dyspnea should not be interpreted in isolation in CTD-ILD.

Serial PFT are the cornerstone of routine monitoring in ILD. In CTD-ILD, the approach to monitoring has been heavily influenced by IPF data with a focus on serial FVC decline and found to predict

earlier mortality in IPF studies.52–55 In RA-ILD, FVC decline is a more powerful prognostic determinant than baseline data56 and in SSc-ILD, serial pulmonary func- tion trends have been predictive of increased mortality in two cohorts,23,57 although serial decline in DLCO and KCO had greater prognostic value than FVC trends. However, there are major confounding factors that undermine the primacy of pulmonary function trends in CTD-ILD in identifying disease progression.

FVC thresholds for significant change are based on PFT reproducibility, with a 10% decline in FVC or a 15% decline in DLCO indicative of true change, as opposed to measurement variability. These thresholds for change have equivalent prognostic value in IPF whether computed as absolute change in percentage predicted values (e.g., a reduction in FVC from 70 to 60% of predicted) or percentage change from baseline (e.g., a reduction in FVC from 2.0 to 1.8 L), with percentage change from baseline more sensitive to change.58 However, uncritical extrapolation from IPF data is problematic in CTD-ILD for three reasons.

- Disease progression is much less prevalent in CTD-ILD than in IPF. Arguing from Bayesian analysis, the ratio of true-positive to false-positive FVC trends in CTD-ILD is substantially reduced, compared with IPF. In IPF, a 10% decline in FVC may occur due to measurement variation or infection but these confounders account for a lower proportion of patients with “significant” FVC decline in IPF than in CTD-ILD because true IPF progression is considerably more frequent than progression of CTD- ILD (with the probable exception of RA-UIP).

- The confounding effect of measurement variability can be minimized by considering FVC and DLCO trends in tan- dem. However, apparent progression of CTD-ILD may reflect worsening of pulmonary comorbidities, with respiratory muscle weakness influencing FVC trends and DLCO change subject to progression of pulmonary vasculopathy. Infection and drug-induced lung disease may also be a more frequent cause of PFT decline in CTD-ILD due to immunosuppressive regimens that are no longer used in IPF.

- To further complicate matters, PFT measurement variation results equally in the overstatement and understatement of change: a 5 to 10% reduction in FVC may represent true disease progression, as shown in IPF, but is more often a false-positive statement of decline in diseases less progressive than IPF. Interpreting marginal trends in FVC can sometimes be facilitated by amalgamating FVC and DLCO trends, with decline defined either as a 10% serial reduction in FVC or a 5-10% reduction in FVC in combination with a 15% reduction in DLCO.57 However, in many

cases, trends fall short of this composite approach but are suggestive, nonetheless.

For all these reasons, PFT trends cannot be viewed with the same confidence as in IPF and should not be interpreted in isolation unless change is definitive (e.g., a 15% decline in FVC supported by DLCO trends) and there is no alternative explanation for PFT decline.

It might be supposed that routine CT monitoring should have a greater role in CTD-ILD than in IPF, due to the difficulties in interpreting other monitoring domains. In some cases, serial CT is highly illuminating in showing clear progression of CTD-ILD, as opposed to worsening pulmonary vasculopathy. However, the subjective detection of change on serial CT is not always straightforward. Serial CT evaluation suffers from a lack of definition of clinically significant change, with subtle change of questionable significance a

frequent observation. Objective monitoring of disease progression using a sophisticated automatic monitoring approach has yielded powerful data in SSc-ILD59 but is not, as yet, available in routine practice. Furthermore, CT has a

significant radiation burden which mitigates against routine serial monitoring in the large subgroup of younger CTD-ILD patients. For this reason alone, it is widely believed that CT should be repeated only in order to adjudicate whether there is true CTD-ILD progression when the integration of sympto- matic change and PFT trends is suggestive but inconclusive. Given these problems, multidisciplinary evaluation is pivotal in identifying CTD-ILD progression in the major patient subgroup in which serial CT evaluation is needed. In many cases, PFT, symptomatic, and CT data are all sugges- tive but inconclusive and a multidisciplinary consensus view is required. This is especially the case in SSc-ILD, in which progression of pulmonary vascular disease is relatively fre- quent, compared with other CTD-ILDs. It might be supposed that selective decline in DLCO provides accurate guidance as to progression of vasculopathy, but DLCO trends are often marginal and may reflect ILD progression. In this scenario, review of change on CT in a multidisciplinary setting, with a focus on the amplitude of change in CT extent and serial reduction in lobar volumes (►Fig. 1), is often illuminating. An isolated CT report of evidence of progression (which is often subtle) is less helpful to the clinician: face-to-face discussion is required.

The role of MDD Is Refining Treatment Goals and Strategies

There is an increasing tendency for rheumatologists to participate in ILD MDD. In one European country, there is a legal requirement for a rheumatologist to be present during MDD (whether or not there is discussion of patients with an established CTD). Management decisions in CTD-ILD are complicated by treatment indications for systemic disease. Rheumatologist participation has particular advantages with regard to two treatment scenarios.

First, in many cases, it is possible to take a global view that treatment decisions should be driven by systemic rather than pulmonary disease, or vice versa. It is difficult for many (but not all) rheumatologists to make isolated judgments on the clinical significance of CTD-ILD, given the need to recon- cile symptoms with PFT and CT findings. Ideally, CTD-ILD patients should be reviewed in a combined clinic involving both a rheumatologist and an ILD clinician, but this is often impracticable. The multidisciplinary forum provides a help- ful forum in which to agree on treatment imperatives.

Second, in those cases in which both CTD-ILD and sys- temic disease require immunomodulation, face-to-face dis- cussion on the choice of agent is often invaluable. For example, mycophenolate mofetil is now widely preferred by ILD clinicians but is often inefficacious in active systemic

RA.60 Rituximab is often a useful treatment for active systemic CTD, but cannot be accessed by ILD clinicians in many countries due to regulatory constraints, despite suggestive data in small cohorts in IM-ILD61 and SSc-ILD.62 Face-to-face

MDD often allows access to rituximab based on approval for systemic indications. In essence, this process consists of the selection of a regimen which is appropriate equally for systemic and pulmonary disease.

Conclusion

In this review, we have highlighted the many roles of multi- disciplinary evaluation in CTD-ILD. In patients meeting IPAF criteria and in other cases with clinical and/or serologic features suggestive of

CTD, a diagnosis of CTD-ILD can often be cemented by integrating the views of a rheumatologist with symptomatic, PFT, and CT data. Multidisciplinary eva- luation facilitates the quantification of CTD-ILD severity, refining prognostic evaluation, and minimizing the limitations of symptom severity, PFT, and CT in isolation. This applies equally to the identification of CTD-ILD progression. MDD of all of these aspects leads logically to discussion of treatment imperatives and strategies, with a more accurate selection of specific agents that address both pulmonary and systemic diseases. It is acknowledged that we argue for broader MDD discussion than is currently routinely per- formed in many ILD expert groups, but there is increasing involvement of rheumatologists in CTD-ILD multidisciplinary evaluation. We argue that this recent change should be strongly supported.

References

1 Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med 2018;6(02):138–153 Review

2 Tansey D, Wells AU, Colby TV, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004;44(06):585–596

3 Bouros D, Wells AU, Nicholson AG, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002;165(12): 1581–1586

4 Park JH, Kim DS, Park IN, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. Am J Respir Crit Care Med 2007;175(07):705–711

5 Tsuchiya Y, Takayanagi N, Sugiura H, et al. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. Eur Respir J 2011;37(06):1411–1417

6 Moua T, Zamora Martinez AC, Baqir M, Vassallo R, Limper AH, Ryu JH. Predictors of diagnosis and survival in idiopathic pulmonary fibrosis and connective tissue disease-related usual interstitial pneumonia. Respir Res 2014;15:154

7 Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneu- monia in rheumatoid arthritis-associated interstitial lung dis- ease. Eur Respir J 2010;35(06):1322–1328

8 Kelly CA, Saravanan V, Nisar M, et al; British Rheumatoid Inter- stitial Lung (BRILL) Network. Rheumatoid arthritis-related inter- stitial lung disease: associations, prognostic factors and physiological and radiological characteristics–a large multicentre UK study. Rheumatology (Oxford) 2014;53(09):1676–1682

9 Yunt ZX, Chung JH, Hobbs S, et al. High resolution computed tomography pattern of usual interstitial pneumonia in rheuma- toid arthritis-associated interstitial lung disease: relationship to survival. Respir Med 2017;126:100–104

10 Douglas WW, Tazelaar HD, Hartman TE, et al. Polymyositis- dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med 2001;164(07):1182–1185

11 Ito I, Nagai S, Kitaichi M, et al. Pulmonary manifestations of primary Sjogren's syndrome: a clinical, radiologic, and pathologic study. Am J Respir Crit Care Med 2005;171(06):632–638

12 Castillo D, Walsh S, Hansell DM, et al; ERICE ILD working group. Validation of multidisciplinary diagnosis in IPF. Lancet Respir Med 2018;6(02):88–89

13 Walsh SLF, Wells AU, Desai SR, et al. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in dif- fuse parenchymal lung disease: a case-cohort study. Lancet Respir Med 2016;4(07):557–565

14 Fischer A, Antoniou KM, Brown KK, et al; "ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD". An official European Respiratory Society/American Thoracic Society research state- ment: interstitial pneumonia with autoimmune features. Eur Respir J 2015;46(04):976–987

15 Luppi F, Wells AU. Interstitial pneumonitis with autoimmune features (IPAF): a work in progress. Eur Respir J 2016;47(06): 1622–1624

16 Oldham JM, Adegunsoye A, Valenzi E, et al. Characterisation of patients with interstitial pneumonia with autoimmune features. Eur Respir J 2016;47(06):1767–1775

17 King TE Jr, Bradford WZ, Castro-Bernardini S, et al; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370(22):2083–2092

18 Richeldi L, du Bois RM, Raghu G, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370(22):2071–2082

19 Gibson GJ. Clinical Tests of Respiratory Function. London: Chap- pell and Hall; 1996:223–224

20 Wells AU, Hansell DM, Rubens MB, Cailes JB, Black CM, du Bois RM. Functional impairment in lone cryptogenic fibrosing alveolitis and fibrosing alveolitis associated with systemic sclerosis: a comparison. Am J Respir Crit Care Med 1997;155 (05):1657–1664

21 Cordier J-F. Organising pneumonia. Thorax 2000;55(04):318–328

22 Burke CM, Glanville AR, Morris AJ, et al. Pulmonary function in advanced pulmonary hypertension. Thorax 1987;42(02): 131–135

23 Goh NS, Hoyles RK, Denton CP, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol 2017;69(08):1670–1678

24 Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pul- monary hypertension and pulmonary function testing in idio- pathic pulmonary fibrosis. Chest 2007;131(03):657–663

25 Steen VD, Graham G, Conte C, Owens G, Medsger TA Jr. Isolated diffusing capacity reduction in systemic sclerosis. Arthritis Rheum 1992;35(07):765–770

26 Broderick A, Fuortes LJ, Merchant JA, Galvin JR, Schwartz DA. Pleural determinants of restrictive lung function and respiratory symptoms in an asbestos-exposed population. Chest 1992;101 (03):684–691

27 Wright PH, Hanson A, Kreel L, Capel LH. Respiratory function changes after asbestos pleurisy. Thorax 1980;35(01):31–36

28 Vincken WG, Elleker MG, Cosio MG. Flow-volume loop changes reflecting respiratory muscle weakness in chronic neuromuscular disorders. Am J Med 1987;83(04):673–680

29 Braun NM, Arora NS, Rochester DF. Respiratory muscle and pulmonary function in polymyositis and other proximal myopa- thies. Thorax 1983;38(08):616–623

30 Gibson GJ, Pride NB, Davis JN, Loh LC. Pulmonary mechanics in patients with respiratory muscle weakness. Am Rev Respir Dis 1977;115(03):389–395

31 Gould GA, Redpath AT, Ryan M, et al. Lung CT density correlates with measurements of airflow limitation and the diffusing capa- city. Eur Respir J 1991;4(02):141–146

32 Hansell DM, Rubens MB, Padley SPG, Wells AU. Obliterative bronchiolitis: individual CT signs of small airways disease and functional correlation. Radiology 1997;203(03):721–726

33 Wells AU, King AD, Rubens MB, Cramer D, du Bois RM, Hansell DM. Lone cryptogenic fibrosing alveolitis: a functional-morphologic correlation based on extent of disease on thin-section computed tomography. Am J Respir Crit Care Med 1997;155(04):1367–1375

34 Antoniou KM, Margaritopoulos GA, Goh NS, et al. Combined pulmonary fibrosis and emphysema in scleroderma-related lung disease has a major confounding effect on lung physiology and screening for pulmonary hypertension. Arthritis Rheumatol 2016;68(04):1004–1012

35 Jacob J, Song JW, Yoon HY, et al. Prevalence and effects of emphysema in never-smokers with rheumatoid arthritis inter- stitial lung disease. EBioMedicine 2018;28:303–310

36 Robbie H, Wells AU, Jacob J, et al. Visual and automated computed tomography (CT) measures of lung volume loss in idiopathic pulmonary fibrosis (IPF). AJR Am J Roentgenol 2019; In pressQ12

37 Devaraj A, Wells AU, Meister MG, Corte TJ, Wort SJ, Hansell DM. Detection of pulmonary hypertension with multidetector CT and echocardiography alone and in combination. Radiology 2010;254 (02):609–616

38 Shin S, King CS, Puri N, et al. Pulmonary artery size as a predictor of outcomes in idiopathic pulmonary fibrosis. Eur Respir J 2016; 47(05):1445–1451

39 Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006;129(03):746–752

40 Kawut SM, O'Shea MK, Bartels MN, Wilt JS, Sonett JR, Arcasoy SM. Exercise testing determines survival in patients with diffuse parenchymal lung disease evaluated for lung transplantation. Respir Med 2005;99(11):1431–1439

41 Leuchte HH, Baumgartner RA, Nounou ME, et al. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. Am J Respir Crit Care Med 2006;173(07):744–750

42 Wells AU, Cullinan P, Hansell DM, et al. Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1994;149(06):1583–1590

43 Marie I, Hachulla E, Chérin P, et al. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum 2002;47 (06):614–622

44 Tashkin DP, Elashoff R, Clements PJ, et al; Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354(25): 2655–2666

45 Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012;156(10):684–691

46 Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest 2014; 145(04):723–728