



## POSITION STATEMENT

**Diagnosis and management of connective tissue disease-associated interstitial lung disease in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand\***

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**ABSTRACT**

**Pulmonary complications in CTD are common and can involve the interstitium, airways, pleura and pulmonary vasculature. ILD can occur in all CTD (CTD-ILD), and may vary from limited, non-progressive lung involvement,**

**to fulminant, life-threatening disease. Given the potential for major adverse outcomes in CTD-ILD, accurate diagnosis, assessment and careful consideration of therapeutic intervention are a priority. Limited data are available to guide management decisions in CTD-ILD. Autoimmune-mediated pulmonary inflammation is considered a key pathobiological pathway in these disorders, and immunosuppressive therapy is generally regarded the cornerstone of treatment for severe and/or progressive CTD-ILD. However, the natural history of CTD-ILD in individual patients can be difficult to predict, and deciding who to treat, when and with what agent can be challenging. Establishing realistic therapeutic goals from both the patient and clinician perspective requires considerable expertise. The document aims to provide a framework for clinicians to aid in the assessment and management of ILD in the major CTD. A suggested approach to diagnosis and monitoring of CTD-ILD and, where available, evidence-based, disease-specific approaches to treatment have been provided.**

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**Key words:** clinical diagnosis and management, collagen vascular disease, connective tissue disease, interstitial lung disease.

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## INTRODUCTION

The connective tissue diseases (CTD) include a variety of disease entities characterized by end-organ damage mediated by immune system overactivity. Pulmonary complications are common and can involve the interstitium, airways, pleura, pulmonary vasculature and chest wall.<sup>1</sup> Interstitial lung disease (ILD) can occur in all CTD (CTD-associated ILD (CTD-ILD)), and may vary from limited, non-progressive lung involvement, to fulminant, life-threatening disease. Given the potential for major adverse outcomes in CTD-ILD, accurate diagnosis, assessment and careful consideration of therapeutic intervention are a priority.

In contrast to well-defined diagnostic criteria and evidence-based treatment recommendations for idiopathic pulmonary fibrosis (IPF), limited data are available to guide management decisions in CTD-ILD.<sup>2,3</sup> Autoimmune-mediated pulmonary inflammation is

considered a key pathobiological pathway in these disorders, with immunosuppressive therapy generally accepted as the cornerstone of treatment for severe and/or progressive CTD-ILD. However, the natural history of CTD-ILD in individual patients can be difficult to predict, and deciding who to treat, when and with what agent can be challenging. Establishing realistic therapeutic goals from both the patient and clinician perspective requires considerable expertise.

This document aims to provide a framework for clinicians to aid in the assessment and management of ILD in the major CTD. Non-ILD and extra-pulmonary manifestations of CTD will not be discussed in detail. A suggested approach to diagnosis and monitoring of CTD-ILD and, where available, evidence-based, disease-specific approaches to treatment have been provided.

## Methods

This position paper highlights important aspects in the diagnosis and treatment of CTD-ILD, with particular reference to Australia and New Zealand. The document is not intended as a treatment guideline. G.J.K. was appointed as the chair of a 26-member panel with expertise in CTD-ILD, including 17 respiratory physicians, two rheumatologists and an immunologist, pathologist, radiologist, physiotherapist, exercise physiologist, respiratory nurse and patient representative.

After initial face-to-face discussion, specific sections were assigned to individual authors for comprehensive literature review. All authors had the opportunity to review all content and referenced articles, and contribute to all sections in subsequent meetings (conducted as both face-to-face and telephone discussions). Summary statements have been provided at the end of each major section. These statements are based on published data where available (with specific references cited) or expert opinion by consensus agreement where evidence is lacking. Two authors (A.S.J. and G.J.K.) compiled and edited the final manuscript that was reviewed and approved by all authors. The committee did not receive any commercial sponsorship and all panel members worked on an honorary basis.

## APPROACH TO DIAGNOSING CTD-ILD

### Clinical diagnosis of CTD

All CTD can be associated with ILD and, when present, accounts for substantial morbidity and mortality.<sup>4</sup> The estimated prevalence of ILD in the major CTD is shown in Table 1. In most cases of CTD-ILD, the underlying CTD is established at the time of diagnosis. However, ILD can be the presenting (*forme fruste*) or only manifestation of an underlying CTD. For example, ILD is the presenting disease manifestation in up to 10% of rheumatoid arthritis (RA) patients, while in clinically amyopathic dermatomyositis (CADM), anti-synthetase syndrome and systemic sclerosis (SSc) sine scleroderma, ILD may persist as the only manifestation of the CTD.<sup>18–22</sup> Therefore, in all patients with ILD it is vital to assess for subtle and non-volunteered features of CTD based on history and clinical examination.

**Table 1** Summary of estimated prevalence, clinical signs and symptoms, manifestations and non-ILD respiratory manifestation in the major CTD

| CTD                | Prevalence of ILD  | Clinical signs and symptoms  | ILD manifestations                                    | Non-ILD respiratory manifestations <sup>5</sup>  |
|--------------------|--|--|---|--|
| SSc <sup>6</sup>   | Detectable: up to 75%<br>Clinically significant: 25–45% <sup>7,8</sup> | Raynaud's phenomenon<br>Sclerodactyly<br>Digital ulcers/pits<br>Telangiectasia<br>Skin thickening<br>GI involvement              | Most common: NSIP<br>Other: UIP, OP                   | PAH<br>Pulmonary lymphoma<br>Aspiration pneumonia  |
| RA <sup>9</sup>    | Detectable: 30–60%<br>Clinically evident: 10–30% <sup>10</sup>         | Polyarticular synovitis<br>Rheumatoid skin nodules   | Most common: UIP<br>Other: NSIP, OP                   | Bronchiectasis,<br>bronchiolitis<br>Rheumatoid lung nodules<br>Pleural disease ± effusion<br>Respiratory muscle weakness |
| IIM <sup>11</sup>  | 30–50% <sup>12,13</sup><br>Up to 80% in anti-synthetase syndrome       | Proximal symmetrical muscle weakness<br>Gottron's sign<br>Gottron's papules<br>Heliotrope rash<br>Shawl sign<br>Mechanic's hands | Most common: NSIP<br>Other: OP, UIP, AIP/DAD          | Respiratory muscle weakness  |
| SLE <sup>14</sup>  | Detectable: up to 30%<br>Clinically evident: 3–11% <sup>15</sup>       | Photosensitive and/or malar rash<br>Oral ulcers<br>Alopecia<br>Serositis   | Most common: NSIP<br>Other: LIP, OP, UIP, FB, AIP/DAD | Pleuritis<br>Diffuse alveolar haemorrhage<br>Respiratory muscle weakness<br>'Shrinking lung syndrome'                    |
| SjS <sup>16</sup>  | 10–30% <sup>8</sup>  | Sicca symptoms<br>Enlarged parotid glands  | Most common: NSIP<br>Other: OP, LIP, UIP, FB          | MALT lymphoma<br>Amyloidosis<br>Bronchiectasis   |
| MCTD <sup>17</sup> | 20–85% <sup>8</sup>  | Swollen hands<br>Synovitis<br>Myositis<br>Acrosclerosis<br>Raynaud's phenomenon  | Most common: NSIP<br>Other: UIP, OP                   | Pleuritis<br>Diffuse alveolar haemorrhage<br>Respiratory muscle weakness<br>Aspiration pneumonia                         |

AIP, acute interstitial pneumonia; CTD, connective tissue disease; DAD diffuse alveolar damage; FB, follicular bronchiolitis; GI, gastrointestinal; IIM, idiopathic inflammatory myopathy; LIP, lymphocytic interstitial pneumonia; MALT, mucosa-associated lymphoid tissue; MCTD, mixed CTD; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PAH, pulmonary arterial hypertension; RA, rheumatoid arthritis; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

A non-exhaustive list of the clinical signs and symptoms associated with the major CTD is presented in Table 1. In practice, a reasonable screening approach would include enquiry for the presence of inflammatory joint pain or stiffness, Raynaud's phenomenon (especially recent onset), rashes, sicca symptoms (dry eyes and/or dry mouth) or skeletal muscle symptoms (e.g. proximal weakness and myalgia), combined with examination for synovitis, cutaneous signs (e.g. mechanic's hands and malar rash) and proximal muscle strength. A rheumatology review may be helpful if symptoms or signs are difficult to interpret or if further investigations are being considered.

International consensus classification criteria for specific CTD are referenced (Table 1) and are a helpful guide for diagnosis. In addition, some patients have 'overlap' features across several diagnoses, and some patients do not fulfil criteria for specific CTD. In the context of ILD, these patients may be considered as

meeting the research criteria for interstitial pneumonia with autoimmune feature (IPAF).

### Serology

Testing for the presence of autoantibodies is an integral step in the diagnostic work up for a suspected CTD and closely interacts with the clinical assessment summarized above. Certain autoantibody profiles are characteristic or strongly suggestive of a particular CTD, can focus clinical assessment for other organ involvement and assist with determining prognosis and treatment. The development of tests for extended autoantibody profiles, such as the myositis-specific autoantibody (MSA) panel, has helped more accurately identify and characterize patients with CTD-ILD, especially when disease manifestations are subtle. Typical radiological findings (such as rapidly progressive organizing pneumonia (OP), characteristic of anti-synthetase

**Table 2** Most common auto-Ab associations in the major CTD

| CTD                              | Auto-Ab  | Clinical associations  |
|----------------------------------|--|--|
| Systemic sclerosis               | ANA  |  |
|                                  | Anti-centromere                                | Strong association with PAH; 'limited' disease                     |
|                                  | Anti-Scl 70 (topoisomerase I)                  | Strong association with ILD; 'diffuse' disease                     |
|                                  | Anti-RNA polymerase I, III                     | Increased risk of renal crisis with concomitant corticosteroid use |
|                                  |  | Not included on most ENA panels                                    |
| RA                               | RF   |  |
|                                  | Anti-CCP                                       | Strong association with RA-ILD                                     |
| Idiopathic inflammatory myositis | ANA  | Associated with high prevalence of ILD                             |
|                                  | Myositis-specific Ab:                          |  |
|                                  | Anti-tRNA synthetase (Jo-1, PL7, PL12, EJ, OJ) |  |
|                                  | MDA5   | May be associated with rapidly progressive ILD                     |
|                                  | Mi2, TIF1 $\gamma$ , NXP2, SAE                 | TIF1 $\gamma$ , NXP2 increased risk of malignancy                  |
|                                  | SRP, HMGCR                                     | IMNM; severe muscle disease  |
|                                  | Myositis-associated Ab:                        | Also detected in other CTD   |
|                                  | PM-Scl, Ro52, Ku                               |  |
| Systemic lupus erythematosus     | ANA  | Present in >95% of cases   |
|                                  | Anti-dsDNA                                     | Titre often correlates with disease activity                       |
|                                  | Anti-Sm, -RNP, -ribosomal P                    |  |
|                                  | Anti-Ro60 (SSA), -Ro52, -La (SSB)              |  |
| Sjögren's syndrome               | ANA  |  |
|                                  | Anti-Ro60 (SSA), -Ro52, -La (SSB)              | Some patients may have a positive RF                               |
| Mixed connective tissue disease  | ANA  |  |
|                                  | Anti-RNP                                       |  |

Ab, antibody; ANA, anti-nuclear antibody; CCP, cyclic citrullinated peptide; CTD, connective tissue disease; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; NXP, nuclear matrix protein; PAH, pulmonary arterial hypertension; PM, polymyositis; RA, rheumatoid arthritis; RA-ILD, RA-associated ILD; RF, rheumatoid factor; RNP, ribonucleoprotein; SAE, serious adverse event.

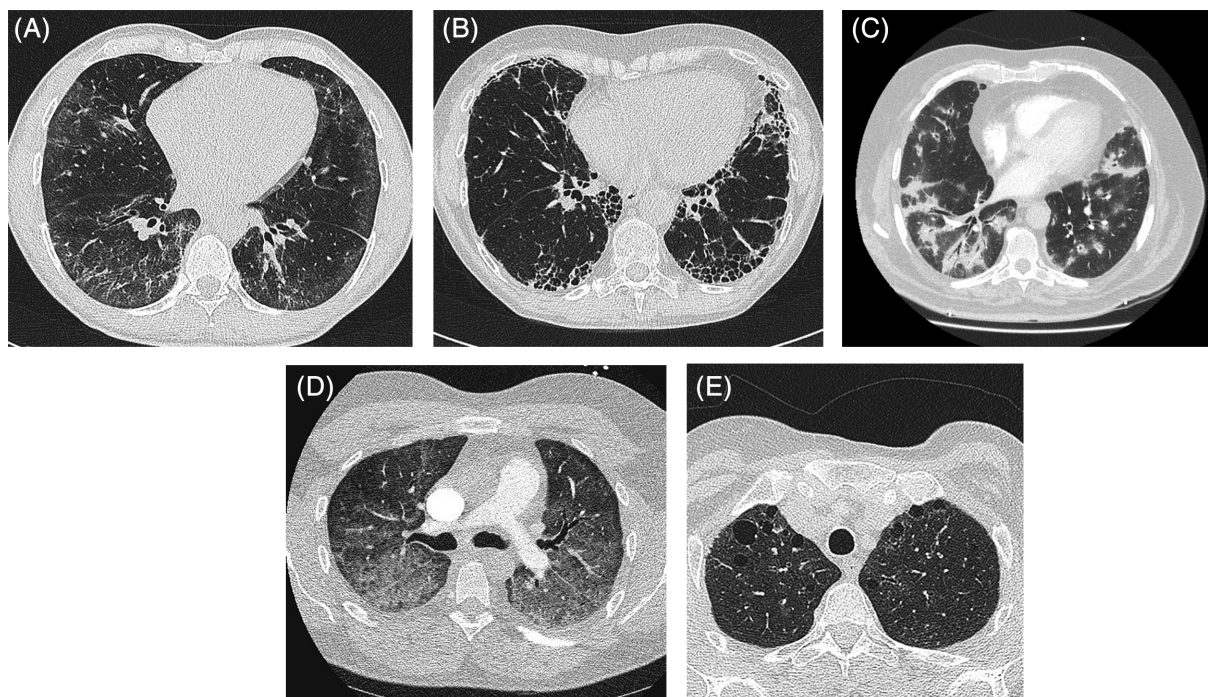
syndrome) may also prompt more detailed serological testing. Major treatment decisions can hinge upon serology, for example, in amyopathic dermatomyositis (DM) where the combination of a positive autoantibody and ILD may be the only evidence of a CTD. Autoantibodies and their disease associations are shown in Table 2 and discussed in more detail in disease-specific sections.

The most common methods for detecting autoantibodies are indirect immunofluorescence (e.g. anti-nuclear antibody (ANA) and double-stranded DNA (dsDNA) autoantibodies), enzyme-linked immunosorbent assay (ELISA; e.g. extractable nuclear antigen (ENA) screen, dsDNA autoantibodies and anti-cyclic citrullinated peptide (CCP) antibody) and line immunoblot (e.g. MSA panel). Individual centres may have access to immunoprecipitation or other bespoke immunological techniques. Each technique has unique strengths and weaknesses, balancing sensitivity, specificity, reproducibility, cost and convenience. Different laboratories employ various techniques and may modify the thresholds used to report 'positive/negative' or 'borderline' results. Thus, serology results must always be interpreted within the clinical context of each patient and not simply taken at 'face value'. The input of a rheumatologist or immunologist on the relative importance of positive results can be helpful in the clinical context.

## Imaging

The principal roles of high-resolution computed tomography (HRCT) in the evaluation of suspected CTD-ILD are to: (i) confirm the presence of ILD and (ii) provide a radiological classification of disease pattern.<sup>23</sup> Almost all radiological patterns can occur in CTD-ILD, with a non-specific interstitial pneumonia (NSIP) pattern the most frequently observed (Table 1, Fig. 1). The exception is RA where the usual interstitial pneumonia (UIP) pattern predominates and is predictive of poorer outcome.<sup>24,25</sup> Other common radiological patterns include OP, lymphocytic interstitial pneumonia (LIP) and some patients may demonstrate a variety of overlapping HRCT patterns.<sup>23,26-28</sup>

Thin-section volumetric computed tomography (CT, 0.5–1.5 mm) is essential for optimal spatial resolution and appreciation of parenchymal detail.<sup>29</sup> Prone sequences help establish whether abnormalities reflect true disease or gravity-dependent change, particularly relevant in the radiological diagnosis of early (or mild) NSIP. Sequences obtained during full expiration highlight features of air-trapping, relevant in the CTD associated with small airways disease (including bronchiectasis, obliterative bronchiolitis and follicular bronchiolitis). Indeed, airways disease can be an early manifestation of RA-associated ILD (RA-ILD), and inspiratory sequences may appear normal or near-normal.<sup>29,30</sup> HRCT also aids the assessment of complications such as infection,



**Figure 1** Common radiological patterns of interstitial lung disease (ILD) in connective tissue disease (CTD). (A) Non-specific interstitial pneumonia (NSIP): ground-glass change and limited reticulation; predominantly basal, subpleural distribution. (B) Usual interstitial pneumonia (UIP): subpleural, basal predominant reticulation with honeycomb change. No ground-glass change, nodules or air-trapping (features 'inconsistent' with radiological UIP). (C) Organizing pneumonia (OP): dense, patchy predominantly peribronchial consolidation affecting the lower lobes bilaterally and symmetrically. (D) Acute interstitial pneumonia (AIP): widespread ground-glass infiltrates in a patient with previously undiagnosed systemic lupus erythematosus (SLE) presenting with acute respiratory failure. (E) Lymphocytic interstitial pneumonia (LIP): variably sized thin-walled cysts. Ground-glass change and centrilobular nodules may also occur (not seen here).

drug-induced pneumonitis, acute exacerbations and malignancy, with increased incidence among certain CTD.<sup>23,27,29–32</sup> HRCT also allows rapid evaluation of ILD extent, largely independent of confounding factors (e.g. concurrent emphysema or pulmonary hypertension (PH)) which may impact pulmonary function tests (PFT).

The syndrome of combined pulmonary fibrosis with emphysema (CPFE) has been described in RA and SSC, sometimes without a significant smoking history.<sup>33</sup> As with idiopathic CPFE, this may represent a distinct clinical phenotype in genetically susceptible individuals with appropriate tobacco exposure. Pleuroparenchymal fibroelastosis (PPFE) is a rare entity that has recently been described in a mixed cohort of CTD patients and may be associated with increased risk of respiratory-related death.<sup>34</sup>

### Histopathology

Similar to radiological patterns, NSIP is the predominant histopathological sub-type found in CTD-ILD (except for RA) and often overlaps with other patterns such as OP and UIP (Table 1).<sup>35–37</sup> Even where radiology may initially demonstrate more inflammatory changes such as ground-glass opacification, CTD-ILD can evolve to a pattern more in-keeping with UIP, with 'honeycomb' cystic lung destruction and irreversible fibrosis. Extent of traction bronchiectasis and extent of honeycombing are independent predictors of mortality

and are more likely to develop if the inflammatory ILD is left untreated or under-treated in its earlier stages.<sup>38</sup>

### Lung biopsy selection and techniques

Lung biopsy is generally not required for the diagnosis of CTD-ILD, with HRCT highly specific for discriminating disease pattern in this population.<sup>37,39</sup> Histopathology can have prognostic implications but this information seldom influences treatment decisions. Lung biopsy may be necessary to exclude non-autoimmune causes for pulmonary infiltrates or nodules (e.g. malignancy) and a reasonable strategy would be to discuss the need for biopsy at a multidisciplinary meeting (MDM) prior to proceeding.

In the rare situations where lung biopsy is considered in CTD-ILD, options include transbronchial lung biopsy using forceps, transbronchial lung cryobiopsy and video-assisted thoracoscopic surgery (VATS) surgical lung biopsy. For investigation of nodules, radiologic-guided core biopsy may be reasonable, but has limited utility outside of this indication. VATS lung biopsy is the gold standard for histopathological sampling of lung parenchyma and provides a diagnostic yield of over 88% in ILD.<sup>2</sup> With an overall morbidity rate of 10–30% and mortality risk of 1–2%, this modality should be reserved for younger patients with well-preserved physiology and fewer comorbidities.<sup>40,41</sup> In

general, the small biopsy size and sampling error of traditional transbronchial biopsy limit its role in the diagnosis of ILD, but may be considered in airway-centred processes such as OP. Cryobiopsy has been shown to have superior diagnostic yield compared with conventional forceps biopsy in studies of mixed ILD populations, with larger tissue sample size and absence of crush artefact.<sup>42</sup> The recently published *Cryobiopsy versus Open Lung Biopsy in the Diagnosis of Interstitial Lung Disease* (COLDICE) study reported high levels of agreement between cryobiopsy and surgical lung biopsy for both histopathological interpretation and MDM diagnoses in patients with difficult to classify ILD who required histopathological evaluation to aid diagnosis.<sup>43</sup> Current American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society (ATS/ERS/JRS/ALAT) IPF diagnostic guidelines do not make recommendations for or against the use of cryobiopsy for ILD diagnosis outside of expert centres.<sup>2</sup> A recent expert consensus statement from the American College of Chest Physicians provides guidance for the procedural aspects of cryobiopsy, without specific recommendations on cryobiopsy application in CTD-ILD.<sup>44</sup>

### Bronchoscopy and lavage

Bronchoscopy with bronchoalveolar lavage (BAL) may be indicated in the CTD-ILD patients with unexplained radiological lung infiltrates. Analysis of BAL cellular composition and microbial cultures can help distinguish possible differential diagnoses including infection, haemorrhage and drug-induced eosinophilic infiltrate. BAL leucocyte differential counts in CTD-ILD have been described in the research setting but seldom influence treatment decisions.<sup>45</sup>

### Multidisciplinary meeting

Comprehensive description of the core features, governance and constitution of the ILD-MDM have recently been detailed in a joint Thoracic Society of Australia and New Zealand (TSANZ)/Lung Foundation Australia position statement.<sup>46</sup> In brief, the ILD-MDM consists of the face-to-face discussion of clinical and diagnostic material by clinicians caring for the patient with respiratory physicians, a radiologist and, if relevant, a histopathologist with expertise in ILD (Fig. 2). Rheumatologists may also play an important role in the ILD-MDM, with CTD-ILD among the most common presentations to the ILD-MDM after IPF.<sup>47</sup>

Specific studies on the role of MDM in CTD-ILD are limited. Walsh *et al.* investigated the agreement between seven ILD-MDM for the diagnosis of 70 ILD cases.<sup>48</sup> Agreement for a diagnosis of CTD-ILD was the highest for any ILD (weighted kappa: 0.73).<sup>48</sup> However, independent clinician agreement before MDM discussion was already high (weighted kappa: 0.76), suggesting that MDM discussion may not be essential if CTD-ILD diagnosis is clear cut. However, MDM also aid the re-classification of previously unrecognized CTD-ILD, mainly from unclassifiable and 'IPF' referrals, with important implications for prognosis and management. The frequency of CTD-ILD diagnosis increased

from 10% to 21% after MDM discussion in a study of 90 consecutive ILD-MDM cases.<sup>49</sup>

With the evolution of ILD nomenclature (including the Fleischner criteria), and the nuances of designating likely histology from HRCT appearances, the ILD-MDM is an increasingly important forum for integrating 'clinical context' with HRCT patterns, informing prediction of disease behaviour and treatment decisions.<sup>50</sup> In addition, in complex CTD-ILD cases, the ILD-MDM may be useful in staging severity and assessing serial change.<sup>51</sup>

### SUMMARY

- Integration of clinical, serological and HRCT findings, coupled with ILD-MDM discussion, is key to confirming an accurate diagnosis of CTD-ILD.<sup>46,51</sup>
- NSIP is the most frequent radiological and histological ILD pattern seen in association with CTD.<sup>23,35-37</sup>
- Lung biopsy generally does not contribute significant additional diagnostic or prognostic information and should be reserved for cases of major diagnostic uncertainty following ILD-MDM discussion.<sup>37,39-41</sup>

### APPROACH TO MANAGEMENT OF CTD-ILD

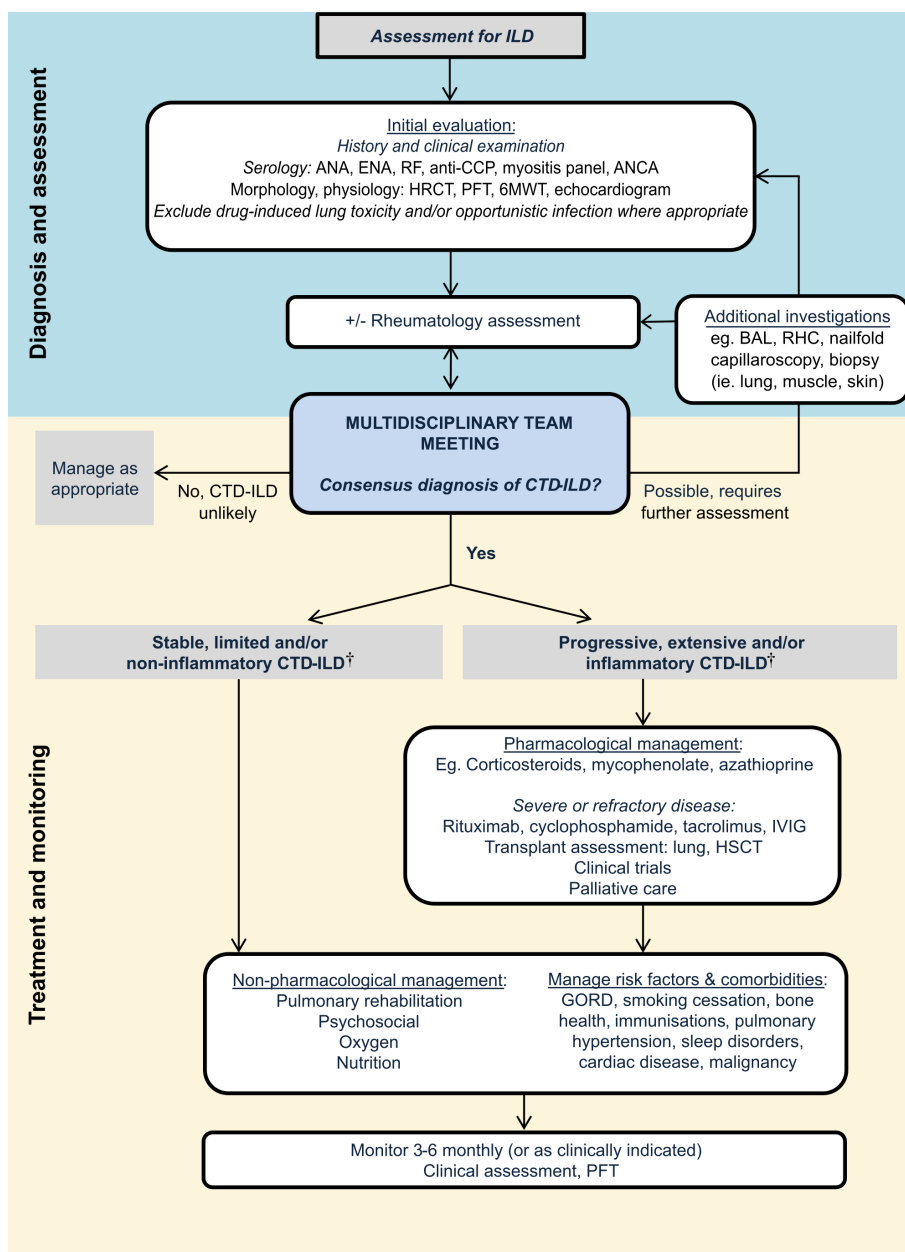
#### General principles of monitoring and treatment

Given the heterogeneous disease course of CTD-ILD, accurate prognostication involving staging of ILD severity and assessment of disease progression is important when making treatment decisions. An understanding of the natural history of the specific CTD-ILD in question also provides important information. For example, whilst SSc-associated ILD (SSc-ILD) may follow a relatively indolent course and require only careful monitoring, myositis-associated ILD (idiopathic inflammatory myopathy-associated ILD (IIM-ILD)) can progress rapidly, necessitating intensive immunosuppressive therapy. Importantly, drug-induced ILD and infection (including opportunistic infection) should always be considered in the setting of new-onset interstitial changes in CTD, particularly in those receiving immunosuppressive therapy.

#### Staging and prognostication

Staging CTD-ILD severity at diagnosis allows survival estimation and establishment of a baseline from which to gauge future change. In addition to clinical examination, baseline investigations typically include PFT, HRCT and echocardiography in certain circumstances (e.g. SSc-ILD).

There is no universally accepted staging system for CTD-ILD, with several different models proposed. The ILD-GAP index (ILD subtype, gender, age and



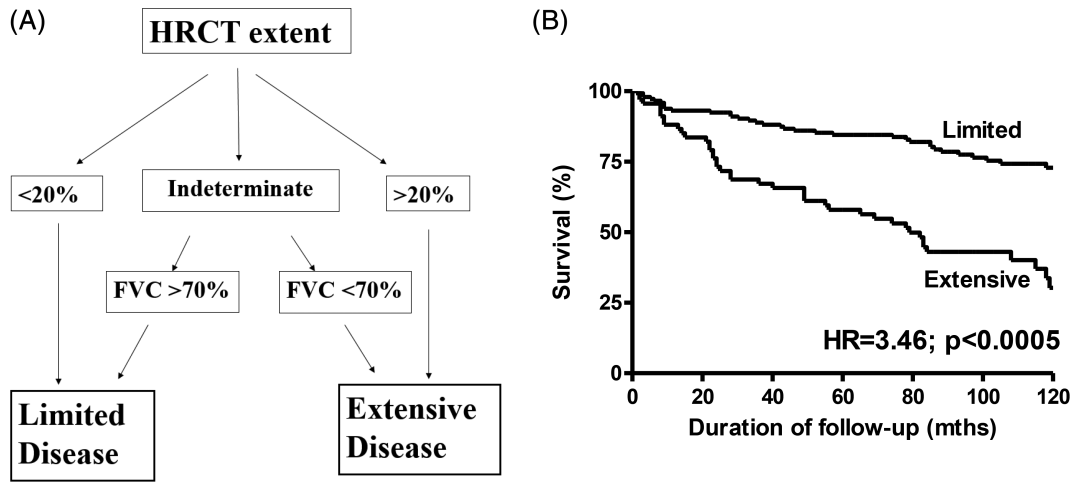
**Figure 2** Suggested algorithm for the diagnosis and management of connective tissue disease-associated interstitial lung disease (CTD-ILD). <sup>†</sup>For detailed discussion, see the section ‘Deciding when to treat’.

pulmonary function tests) has been validated across a range of ILD, including CTD-ILD.<sup>52</sup> An important exception appears to be IIM-ILD, where the ILD-GAP model is a poor predictor of mortality risk.<sup>53</sup> In SSC-ILD, an algorithm based on HRCT appearances and PFT defines ‘limited’ or ‘extensive’ disease (Fig. 3).<sup>54</sup> Both staging systems demonstrate similar survival estimates for patients with more severe or extensive CTD-ILD, identifying a population that may benefit from treatment intervention.

Disease trajectory is a powerful prognostic determinant and longitudinal measurement of PFT is vital to monitoring ILD progression.<sup>55,56</sup> A decline in forced vital capacity (FVC)  $\geq 10\%$  and/or diffusing capacity for carbon monoxide (DL<sub>CO</sub>)  $\geq 15\%$  on serial measures indicates clinically significant disease progression and

is associated with increased mortality risk.<sup>38,56–58</sup> However, even ‘marginal’ declines (e.g.  $<10\%$  FVC) can represent progressive ILD in the appropriate context, particularly if associated with deterioration in symptoms and other measures (e.g. oxygen saturation and 6-min walk distance).<sup>59</sup> A number of unique confounders should be kept in mind when interpreting PFT in CTD-ILD, including concomitant PH contributing to a reduced DL<sub>CO</sub>, and the presence of muscular weakness, pleural disease and/or thoracic skin thickening (particularly in diffuse cutaneous SSC) that can reduce lung volumes independent of the ILD.

HRCT provides important diagnostic and staging information, but serial HRCT is not recommended to routinely monitor disease progression. Repeat HRCT imaging may be useful to corroborate a decline in PFT



**Figure 3** (A) A simple staging system for systemic sclerosis-associated interstitial lung disease (SSc-ILD). (B) Survival curves for SSc-ILD patients with ‘limited’ versus ‘extensive’ disease (hazard ratio (HR) = 3.46;  $P < 0.0005$ ) (Adapted from Goh *et al.*,<sup>54</sup> with permission).

and exclude other causes of deterioration (e.g. infection, pulmonary embolism and malignancy). Computer-based quantitative CT analysis and molecular and genetic biomarkers as objective measures of disease prognosis are exciting and evolving research areas, not yet validated for clinical use.<sup>60,61</sup>

*Deciding when to treat*

Accurately distinguishing patients with inherently stable CTD-ILD who can be carefully observed without treatment, from those at risk of progression requiring therapy is one of the most challenging aspects of CTD-ILD management.<sup>62,63</sup> Whilst the goal of treatment in most cases of CTD-ILD is to achieve stability and prevent further progression, a number of important exceptions to this rule exist and are discussed in more detail below. The decision to treat and the intensity of treatment are influenced by a variety of factors including the CTD subtype, ILD severity, observed disease trajectory and mitigating patient factors. Progressive ILD,

particularly in the context of recent onset systemic CTD manifestations, is another important factor influencing treatment decisions. The presence of extra-pulmonary CTD manifestations (e.g. active synovitis in RA for which mycophenolate and azathioprine are largely ineffective) may also impact treatment strategies, highlighting the importance of multidisciplinary involvement between respiratory physicians, rheumatologists and immunologists. Referral to an ILD expert centre may be useful when deciding who, when and how to treat. Treatment approaches based on estimated disease behaviour, coupled with treatment goals and monitoring strategies, have been adapted from the idiopathic interstitial pneumonias (IIP) and summarized in Table 3.

Treatment strategies are largely drawn from studies in SSc-ILD and extrapolated to the other CTD-ILD. Whilst reasonable in the absence of specific evidence, caution is required, especially in more progressive CTD-ILD, such as IIM-ILD. CTD-ILD that is limited (HRCT extent <20% and/or FVC >70%) with stable lung

**Table 3** Disease behaviour, treatment goals and intervention in CTD-ILD

| Disease behaviour  | Treatment goal                        | Intervention and monitoring  |
|--|---------------------------------------|--|
| Reversible, self-limited                                   | Achieve regression                    | Short-term (3–6 months) observation to confirm disease regression  |
| Reversible, with risk of progression                       | Achieve regression and then stabilize | Intensive/higher dose treatment with short-term monitoring to ensure response. Then, rationalize to maintenance treatment and long-term observation to ensure stability    |
| Stable, risk of progression                                | Maintain status                       | Maintenance treatment. Monitor for disease progression   |
| Progressive, irreversible with potential for stabilization | Stabilize                             | Intensive/higher dose treatment and then rationalize to maintenance treatment. Short-term monitoring to ensure response and then long-term observation to ensure stability |
| Progressive, despite treatment                             | Slow disease progression              | Rescue therapy<br>Trials<br>Transplantation<br>Palliative/best supportive case   |

Adapted from Travis *et al.*,<sup>64</sup> with permission.  
CTD-ILD, connective tissue disease-associated interstitial lung disease.



**Table 4** Common immunosuppressive therapies utilized in CTD-ILD

| Medication and mechanism   | Dosage  | Adverse effects   | Screening and monitoring  |
|--|---|---|---|
| <p>Corticosteroids</p> <p>Bind to the intracellular glucocorticoid receptor → inhibits cytokine transcription →</p> <p>(1) ↓ T cells (IL2 inhibited)</p> <p>(2) Eosinophil apoptosis (directly or by inhibition of IL5)</p> <p>(3) Macrophage inhibition (blocking IL1 and TNF-α)</p> <p>(4) Leucocytosis</p> <p>B cells are not significantly inhibited</p> | <p>Start 0.5 mg/kg/day. Aim to taper down to 10–20 mg maintenance</p>   | <p>Diabetes</p> <p>Weight gain</p> <p>Hypertension</p> <p>Myopathy</p> <p>Osteoporosis</p> <p>Accelerated atherosclerosis</p> <p>Sleep disturbance</p> <p>Cataracts</p> <p>Glaucoma</p> <p>Dyspepsia</p> <p>Pregnancy risk category A</p>                                 | <p>BP</p> <p>Serum glucose</p> <p>Lipid profile</p> <p>Eye examination</p> <p>Bone densitometry</p>                     |
| <p>AZA</p> <p>Inhibits DNA and RNA synthesis in mainly T cells but also B cells</p>  | <p>2.0–2.5 mg/kg/day if TPMT within normal limits</p>   | <p>Bone marrow suppression</p> <p>GI intolerance</p> <p>Hepatotoxicity</p> <p>Increased malignancy risk (skin and lymphoproliferative)</p> <p>Avoid allopurinol</p> <p>Pregnancy risk category D</p>  | <p>TPMT</p> <p>FBC and LFT</p>  |
| <p>MMF and enteric-coated mycophenolate sodium</p> <p>Inhibits DNA synthesis in T and B cells</p>  | <p>MMF: start 500 mg bd, titrating to 2–3 g daily (in two divided doses)</p> <p>MMF 500 mg = enteric-coated mycophenolate sodium 360 mg</p> | <p>Diarrhoea</p> <p>Bone marrow suppression</p> <p>Hepatotoxicity</p> <p>Increased malignancy risk (skin and lymphoproliferative)</p> <p>Progressive multifocal leucoencephalopathy</p> <p>Pregnancy risk category D contraindicated in pregnancy (category D)</p>        | <p>FBC, LFT, renal function</p>   |
| <p>Cyclophosphamide</p> <p>Alkylating agent toxic to all human cells to differing degrees with haematopoietic cells forming a sensitive target</p>   | <p>600 mg/m<sup>2</sup>, maximum dose 1000 mg</p> <p>Monthly for maximum 6 months</p>   | <p>Toxicity to bladder and gonads</p> <ul style="list-style-type: none"> <li>• &lt;250–300 mg/kg cumulative dose to avoid gonadal toxicity</li> <li>• &lt;360 mg/kg cumulative to minimize risk of malignancy</li> </ul> <p>Contraindicated in pregnancy (category D)</p> | <p>Maintain adequate fluid intake to avoid bladder toxicity</p> <p>Monthly urinalysis</p> <p>FBC and LFT</p>            |
| <p>Tacrolimus</p> <p>Prevents calcineurin-dependent gene transcription in T cells</p>  | <p>Start 1 mg bd titrating by 1–2 mg daily with at least 7 days between adjustments. Aim for 12 h trough level 5–8 ng/mL</p>                | <p>Increased vascular constriction → ↑BP, ↓ renal perfusion</p> <p>Contraindicated in pregnancy (category D)</p>  | <p>Trough levels 10–14 days after initiating and at regular intervals</p> <p>Monitor BP, BGL, FBC, EUC, LFT, lipids</p> |
| <p>Rituximab</p> <p>B-cell depletion by targeting CD20 lasting 6–9 months</p>  | <p>Initiation: two 1 g infusions, 2 weeks apart</p> <p>Maintenance: 1 g every 6–12 months</p>   | <p>Hepatitis B reactivation</p> <p>Should not be taken in pregnancy (category C)</p> <p>Hypogammaglobulinaemia</p>  | <p>Screen for hepatitis B (surface antigen and core antibody)</p>   |
| <p>Methotrexate</p> <p>Inhibits dihydrofolate reductase</p>  | <p>Start 5–15 mg/week, escalating by 5 mg/month to maximum 25–30 mg/week</p>  | <p>Pulmonary toxicity</p> <p>Hepatotoxicity</p> <p>Bone marrow suppression</p> <p>Alopecia</p>  | <p>FBC, LFT, EUC</p>  |

Continued

**Table 4** Continued

| Medication and mechanism | Dosage | Adverse effects  | Screening and monitoring |
|--------------------------|--------|--|--------------------------|
|                          |        | Mouth ulcers<br>Contraindicated in pregnancy<br>(category D) |                          |

AZA, azathioprine; bd, twice daily; BGL, blood glucose level; BP, blood pressure; CTD-ILD, connective tissue disease-associated interstitial lung disease; EUC, electrolyte and urea concentration; FBC, full blood count; GI, gastrointestinal; LFT, liver function test; MMF, mycophenolate mofetil; TNF, tumour necrosis factor; TPMT, test for thiopurine methyltransferase.

function over time can generally be closely monitored with serial PFT and clinical assessment (Fig. 3A). In contrast, extensive and/or progressive ILD usually warrants treatment.<sup>56,58,65</sup> However, extensive ILD alone is not an indication for therapy with established fibrosis with stable lung function and symptoms less likely to respond to immunosuppression and careful monitoring without pharmacotherapy may be appropriate. A suggested algorithm for the broad management of CTD-ILD is shown in Figure 2.

### Pharmacological/immunosuppressive treatment

Immunosuppression is the mainstay of pharmacotherapy in CTD-ILD, aiming to reduce inflammation, minimize progression to established fibrosis and permanent loss of lung function.<sup>62</sup> The general mechanism of action is to interfere with critical pathways in the inflammatory cascade including B- and T-cell function, and inhibit pro-inflammatory cytokines, although precise mechanisms are poorly understood.<sup>66</sup> The major classes of immunosuppressive medications, their mechanism of action and potential adverse effects are summarized in Table 4. Prior to commencement of immunosuppressive therapy, screening for active/latent microorganisms and organ dysfunction is recommended due to the increased risk of new or reactivated infection (e.g. tuberculosis (TB) and hepatitis) and side effects.<sup>67</sup>

The intensity of immunosuppressive therapy is tailored to the individual CTD, acuity of ILD presentation, therapeutic expectations and patient factors. For example, rapidly progressive ILD as seen in IIM and systemic lupus erythematosus (SLE) often presents with a radiological pattern of OP or diffuse alveolar damage (DAD), suggesting a predominantly inflammatory process. In such situations, intensive immunosuppression with pulse intravenous (IV) methylprednisolone, IV cyclophosphamide or rituximab may be required with the expectation of achieving reversal of inflammation and minimizing permanent lung damage.<sup>62,63</sup> In contrast, SSc-ILD may be more slowly progressive and lower dose maintenance therapy to achieve stabilization rather than major improvement is a realistic therapeutic goal. Specific treatment approaches are discussed in more detail in relevant disease sections and currently available evidence from treatment trials is summarized in Table 5.

Anti-fibrotic therapy has recently been found to be of benefit in CTD-ILD. Annual rate of decline in FVC was lower in patients with SSc-ILD and progressive fibrosing-ILD who received nintedanib compared with placebo in

the *Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS)* and *Nintedanib in Progressive Fibrosing Lung Disease (INBUILD)* trials, respectively.<sup>85,86</sup> INBUILD included a range of fibrosing ILD, incorporating 170 patients with 'autoimmune' ILD, including RA-ILD, SSc-ILD and mixed CTD (MCTD)-associated ILD (MCTD-ILD). Although not powered to provide evidence for a benefit of nintedanib in specific diagnostic subgroups, results suggest that nintedanib reduces the rate of ILD progression (measured by FVC decline) in patients with chronic, progressive fibrosing ILD.<sup>87</sup> Pirfenidone has also shown potential benefit in patients with progressive unclassifiable ILD, including a subgroup with IPAF. Slower disease progression was observed in study participants receiving pirfenidone compared with placebo over 24 weeks.<sup>88</sup> Whilst encouraging, neither nintedanib nor pirfenidone has regulatory approval for the treatment of CTD-ILD in Australia or New Zealand at this time and the exact role of these agents (including patient selection, timing and combination with immunosuppressive therapy) for CTD-ILD remains to be determined.

### Special considerations

Identification of patients at risk of infectious complications is prudent prior to commencement of immunosuppressive therapy. Screening for latent TB infection (LTBI) and hepatitis B is the most well recognized, while hepatitis C, human immunodeficiency virus (HIV) and strongyloides infection should be considered on an individual patient basis.<sup>67,89,90</sup>

#### *Latent TB infection*

The lifetime risk of reactivation in LTBI is approximately 5–10% and increases with immunosuppressive therapy. The risk of TB reactivation increases by up to 25-fold, highest in the first 12 weeks, after commencement of tumour necrosis factor (TNF) inhibitors (e.g. infliximab and adalimumab). Thus, LTBI screening with an interferon-gamma release assay (IGRA) or Mantoux tuberculin skin test (TST) is recommended in all patients where TNF inhibitors are being considered.<sup>91</sup> Patients with LTBI should be treated prior to commencement of TNF inhibitor therapy, which reduces the incidence of TB reactivation by more than 80%.<sup>68,89</sup>

LTBI screening/treatment for other immunosuppressive medications is less clear. Studies have reported a seven-fold increased risk of TB reactivation in patients on corticosteroids.<sup>69</sup> Evidence to recommend LTBI treatment for all patients is currently insufficient, but it is reasonable to evaluate overall risk (steroid dose,

**Table 5** Important treatment trials in CTD-ILD

| Study  | Study design   | Intervention   | Outcome  |
|--|--|--|--|
| Systemic sclerosis<br>Scleroderma Lung Study <sup>68</sup> | Prospective RCT<br><i>n</i> = 158<br>Duration: 12 months                               | Oral CYC (up to 2 mg/kg daily) vs placebo  | Mean absolute improvement in FVC at 12 months of 2.53%, favouring CYC, greater frequency of AE in the CYC arm  |
| FAST study <sup>69</sup>                                   | Prospective RCT<br><i>n</i> = 45<br>Duration: 12 months                                | IV CYC (600 mg/m <sup>2</sup> , monthly for six doses) + low-dose prednisolone (20 mg alternate days) followed by AZA (2.5 mg/kg/day; max 200 mg) vs placebo | Trend to improvement FVC (4.19%; <i>P</i> = 0.08) in the active treatment arm, although statistically non-significant  |
| BUILD 2 (Bosentan) <sup>70</sup>                           | Prospective RCT<br><i>n</i> = 163<br>Duration: 12 months                               | Bosentan 125 mg bd vs placebo  | Negative primary end point with no difference in 6MWD between the groups<br>No increase in SAE in the active treatment group   |
| Scleroderma Lung Study II <sup>71</sup>                    | Prospective RCT<br><i>n</i> = 142<br>Duration: 24 months                               | MMF 1.5 g bd vs oral CYC (up to 2.0 mg/kg/day) for 12 months followed by placebo for 12 months   | Significant improvement in FVC from baseline in both arms (2.2% and 2.9%: MMF vs CYC), with no difference in FVC change between the groups   |
| LOTUSS (pirfenidone) <sup>72</sup>                         | Randomized, open label<br><i>n</i> = 63<br>Duration: 16 weeks                          | Comparison of two pirfenidone up-titration regimens: 2-week titration vs 4-week titration, to a maintenance dose of 801 mg tds                               | Greater frequency of AE in the CYC group<br>'Acceptable' tolerability profile, although a longer up-titration may be associated with better tolerability   |
| Pomalidomide (CC-4047) <sup>73</sup>                       | Prospective RCT<br><i>n</i> = 23<br>Duration: 12 months                                | Pomalidomide 1 mg/day vs placebo   | Negative co-primary end points with no difference in FVC, mRSS or GI symptoms at 52 weeks  |
| faSScinat <sup>74</sup>                                    | Prospective RCT<br><i>n</i> = 87<br>Duration: 48 weeks                                 | Tocilizumab 162 mg subcutaneous weekly vs placebo  | Enrolment discontinued early due to difficult recruitment  |
| SENSCIS (nintedanib) <sup>75</sup>                         | Prospective RCT<br><i>n</i> = 576<br>Duration: 12 months                               | Nintedanib 150 mg bd vs placebo  | Negative secondary end point with no change in FVC or DL <sub>CO</sub> from baseline to 48 weeks   |
| Rituximab <sup>76</sup>                                    | Open-label, comparative study<br><i>n</i> = 51<br>Duration: 4 years (range: 1–7 years) | Rituximab ( <i>n</i> = 33) vs conventional immunosuppression (MMF, AZA or MTX) ( <i>n</i> = 18)  | Positive primary end point with reduced annual rate of change in FVC in subjects receiving nintedanib compared to placebo (–52.4 mL vs –93.3 mL per year; <i>P</i> = 0.04)   |
| SCOT study <sup>77</sup>                                   | Randomized, open-label<br><i>n</i> = 75<br>Duration: 54 months                         | Myeloablative stem cell transplantation ( <i>n</i> = 36) vs IV CYC ( <i>n</i> = 39)  | At 2 years, improvement in FVC compared to baseline in rituximab group, with no change in FVC in conventional immunosuppression group<br>Positive composite primary end point (incorporating death, event-free survival, FVC |

Continued

Table 5 Continued

| Study                                       | Study design  | Intervention   | Outcome   |
|---|---|--|---|
| ASTIS study <sup>78</sup>                   | Randomized, open-label<br><i>n</i> = 156<br>Duration: 5.8 years | Autologous stem cell transplantation ( <i>n</i> = 79) vs IV CYC ( <i>n</i> = 77)   | and mRSS) favouring stem cell transplantation<br>Positive primary end point (death or persistent major organ failure) favouring stem cell transplantation<br>Increased stem cell treatment-associated mortality in the first 12 months<br>Positive primary end point (improvement in mRSS or FVC) favouring stem cell transplantation |
| ASSIST study <sup>79</sup>                  | Randomized, open-label<br><i>n</i> = 19<br>Duration: 12 months  | Non-myeloablative stem cell transplantation ( <i>n</i> = 10) vs IV CYC ( <i>n</i> = 9)   | Fifty percent of treated group improved or had stable lung function   |
| RA<br>Song <i>et al.</i> <sup>80</sup>      | Retrospective review<br><i>n</i> = 84<br>Median f/u: 33 months  | All had RA with UIP. Forty-one percent received glucocorticoids ± immunosuppression due to poor baseline lung function or progressive RA with UIP<br>MMF (1–1.5 g bd)                                | Trend to improvement in FVC following MMF commencement, with reduction in prednisolone requirement  |
| Fischer <i>et al.</i> <sup>81</sup>         | Retrospective review<br><i>n</i> = 18<br>Median f/u: 2.5 years  | Rapidly progressive IIM-ILD ( <i>n</i> = 10); IV CYC IIM-ILD but less rapidly progressive ( <i>n</i> = 10)   | Stabilization in IIM-ILD following IV CYC   |
| IIM<br>Schnabel <i>et al.</i> <sup>82</sup> | Prospective open label<br><i>n</i> = 20<br>Median f/u 35 months | Rapidly progressive IIM-ILD ( <i>n</i> = 10); IV CYC IIM-ILD but less rapidly progressive ( <i>n</i> = 10)   | Fifty percent mortality rate at 3 months  |
| Kameda <i>et al.</i> <sup>83</sup>          | Prospective open label<br><i>n</i> = 27                         | Rapidly progressive IIM-ILD ( <i>n</i> = 10); IV CYC (10–30 mg/kg every 3–4 weeks), prednisolone (>0.5 mg/kg/day) and cyclosporine A (2–4 mg/kg/day)<br>AZA ( <i>n</i> = 66)<br>MMF ( <i>n</i> = 44) | Improved FVC% and DL <sub>co</sub> % predicted in AZA group<br>Improved FVC% predicted in MMF group<br>Lower prednisolone dose in both groups<br>More frequent AE in AZA group  |
| Huapaya JA <i>et al.</i> <sup>148</sup>     | Retrospective review<br><i>n</i> = 110<br>f/u: 24–60 months     |  |   |

6MWD, 6-min walk distance; AE, adverse event; ASSIST, American Scleroderma Stem Cell versus Immune Suppression Trial; ASTIS, Autologous Stem cell transplantation; AZA, azathioprine; bd, twice daily; CTD-ILD, connective tissue disease-associated ILD; CYC, cyclophosphamide; DL<sub>co</sub>, diffusing capacity for carbon monoxide; f/u, follow-up; FVC, forced vital capacity; GI, gastrointestinal; IIM, idiopathic inflammatory myopathy; IIM-ILD, IIM-associated ILD; ILD, interstitial lung disease; IV, intravenous; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; MITX, methotrexate; *n*, number; RA, rheumatoid arthritis; RCT, randomized controlled trial; SAE, serious AE; SCOT, Scleroderma: Cyclophosphamide or Transplantation trial; SENSICIS, Safety and Efficacy of Nintedanib in Systemic Sclerosis; tds, three times daily; UIP, usual interstitial pneumonia.

concomitant immunosuppressive medications, exposures and background incidence), and consider LTBI testing and treatment on an individual basis.<sup>90</sup>

### Hepatitis B

Hepatitis B virus (HBV) reactivation associated with immunosuppressive therapy is associated with significant morbidity and mortality. The American Gastroenterological Association guidelines on the prevention and treatment of HBV reactivation during immunosuppressive drug therapy stratify patients into high-, moderate- or low-risk groups based on the serological pattern (e.g. HBV surface antigen positivity) and immunosuppressive agent.<sup>92</sup> Expert hepatology opinion is strongly recommended if active or previous HBV is detected.<sup>89,90</sup>

### Pneumocystis jirovecii

*Pneumocystis jirovecii* pneumonia (PJP) is a potentially life-threatening infection, most prevalent in patients receiving high-dose glucocorticoids combined with other immunosuppressive agents. There are published guidelines for the use of PJP prophylaxis in HIV, cancer and solid organ transplant recipients.<sup>71</sup> No guidelines exist for CTD patients on immunosuppression, but is an important consideration given the generally long-term nature of immunosuppressive therapy in CTD.<sup>75,93</sup> It is reasonable to recommend prophylaxis (e.g. sulfamethoxazole and trimethoprim) in patients receiving sustained daily corticosteroids of 20 mg/day or greater. Prophylaxis in the context of other immunosuppressants is less clear but should be considered in patients on combinations of immunosuppressants despite lower doses of prednisolone.

## SUMMARY

- Treatment decisions in CTD-ILD are influenced by CTD diagnosis and duration since diagnosis, ILD severity, disease trajectory, extra-pulmonary CTD manifestations and individual patient factors.
- Progressive CTD-ILD with a predominant inflammatory component (determined following clinical and radiological evaluation) may be amenable to significant reversal with appropriate intensive immunosuppression.<sup>62,94</sup>
- Progressive and/or severe CTD-ILD with a predominant fibrotic component typically do not regress significantly with intensive immunosuppression, although stabilization may be achieved with low-dose corticosteroids, with or without a steroid-sparing immunosuppressive agent. New data support the potential role for anti-fibrotic therapy in such cases, although this is not yet approved for use in Australia or New Zealand.<sup>85-87</sup>
- Serial PFT is the cornerstone of CTD-ILD monitoring, including response to treatment.<sup>38,55-57</sup>
- Evaluation for latent infection (e.g. TB and hepatitis) and appropriate opportunistic infection prophylaxis should be considered on an individual patient basis prior to initiation of immunosuppressive therapy.

## SPECIFIC CTD-ILD

### Systemic sclerosis

SSc (also known as scleroderma) is characterized by autoimmunity, fibrosis of the skin and internal organs, and vasculopathy. Pulmonary complications, including ILD and pulmonary arterial hypertension (PAH), are the leading causes of morbidity and mortality in SSc.<sup>77,95</sup> Whilst ILD may occur in up to 80% of SSc patients, only 25–30% have progressive disease and the key challenge is identifying patients at risk of disease progression and likely to benefit from treatment, whilst avoiding unnecessary drug toxicities in indolent disease.<sup>79</sup>

Risk factors for developing severe, progressive SSc-ILD include: (i) SSc disease duration of less than 3 years<sup>78,96</sup>; (ii) diffuse cutaneous SSc<sup>96</sup>; (iii) presence of anti Scl-70/DNA topoisomerase 1 autoantibodies<sup>96</sup>; (iv) severe gastro-oesophageal reflux disease (GORD)<sup>97,98</sup>; (v) extensive ILD<sup>54</sup>; and (vi) declining lung function.<sup>55,56,58</sup> Extent of ILD severity, traditionally quantified by FVC and DL<sub>CO</sub>, is the most important factor, especially in the early stages of disease. The risk of developing ILD is greatest in the first few years after SSc symptom onset, but patients can still progress after this 'at-risk' period.<sup>99</sup> Vigilance for disease progression must always be maintained, with declining lung function associated with increased mortality.<sup>78,100,101</sup>

A simple staging system, incorporating semi-quantitative assessment of disease extent on HRCT and FVC, classifies patients into limited and extensive disease (Fig. 3A).<sup>54</sup> Patients who have <20% or ≥20% disease on HRCT are classified as limited or extensive disease, respectively. If HRCT extent is 'indeterminate', an FVC threshold of above or below 70% predicted is used to distinguish limited versus extensive disease, respectively. This approach has been validated in other SSc-ILD cohorts and provides greater prognostic insight than either HRCT extent or FVC measures alone (Fig. 3B).<sup>65</sup>

The goal of treatment in most cases of severe and/or progressive SSc-ILD is to achieve disease stabilization, rather than major reversal. The use of corticosteroids remains debatable, but when used, dosage should be minimized (<10–15 mg/day), to reduce the risk of side effects and SSc renal crisis. The *Scleroderma Lung Study I* (SLS I) demonstrated modest improvements in lung function, dyspnoea and health-related quality of life (HRQoL) with cyclophosphamide, administered as either a monthly infusion or daily oral dose for 12 months.<sup>102,103</sup> Although the latest European League Against Rheumatism (EULAR) recommendations advocate for the use of cyclophosphamide in SSc-ILD, this is now outdated. Instead, mycophenolate mofetil (MMF) has increasingly been the first drug of choice following the findings from the *Scleroderma Lung Study II* (SLS II).<sup>104</sup> Whilst the beneficial effect on lung function was similar between oral MMF and oral cyclophosphamide given over 24 months, MMF was associated with better tolerability and less adverse effects.<sup>105</sup> However, in patients with rapidly progressive disease, IV cyclophosphamide is still considered the first drug of choice with a quicker onset of action

compared to MMF. In these cases, IV cyclophosphamide could be given monthly for 6 months as the 'induction phase' of treatment, followed by MMF in the 'consolidation phase' of treatment.

The exact duration of ongoing maintenance therapy remains unclear. In the SLS I study, the benefits of cyclophosphamide were lost 12 months after the cessation of treatment.<sup>102</sup> Long-term follow-up of SLS I and SLS II patients (median follow-up of 8 years) demonstrated no difference in survival between cyclophosphamide or MMF, and patients on placebo.<sup>55</sup> It is likely that more than 2 years of immunosuppression is required to sustain improvements in lung function and symptoms with longer term studies required. An observational study of 30 SSc-ILD patients receiving 24 months of IV cyclophosphamide followed by ongoing low-dose immunosuppression (azathioprine, methotrexate (MTX) or MMF) demonstrated sustained improvement in lung function in the ensuing 5 years and no significant adverse events.<sup>106</sup>

The SENSICIS trial demonstrated a reduced decline in FVC in SSc-ILD patients on nintedanib compared with placebo (−52.4 vs −93.3 mL/year, respectively,  $P = 0.04$ ), but does not support nintedanib as a substitution for immunotherapy in SSc-ILD.<sup>85</sup> The magnitude of benefit depended on MMF use, suggesting the potential benefit of MMF on lung function.<sup>85</sup> Furthermore, there were no benefits reported with HRQoL measures or modified Rodnan skin score (mRSS) and nintedanib should not be considered a disease-modifying agent for SSc.<sup>85</sup> It remains unclear if nintedanib should be used following or together with immunosuppressive therapy. The U.S. Food and Drug Administration recently approved nintedanib for the treatment of SSc-ILD, but is not yet approved for this indication in Australia or New Zealand.

Several additional therapeutic options including pirfenidone, tocilizumab and rituximab are currently being evaluated for SSc-ILD.<sup>107</sup> Tocilizumab, an anti-IL6 monoclonal antibody, has recently been investigated in a phase III study of SSc patients, including 31% with ILD (NCT02453256).<sup>108</sup> Preliminary analysis demonstrated preservation of FVC over 48 weeks, less decline in FVC compared with placebo and improvements of fibrosis as assessed by HRCT with final analysis awaited.<sup>109</sup>

### Stem cell transplantation for SSc-ILD

There are no stem cell trials in SSc-ILD *per se*, but secondary lung function end points in broader SSc studies are interesting. Two randomized trials of non-myeloablative autologous haematopoietic stem cell transplant (HSCT)—the *American Scleroderma Stem Cell versus Immune Suppression Trial* (ASSIST) and *Autologous Stem cell transplantation* (ASTIS) trial—reported less SSc disease progression with HSCT compared with cyclophosphamide.<sup>110,111</sup> ASTIS also demonstrated superior event-free survival, overall survival and improvement in FVC and total lung capacity (TLC) over a median follow-up time of 5.8 years.<sup>111</sup> The *Scleroderma: Cyclophosphamide or Transplantation* (SCOT) trial compared myeloablative autologous HSCT to cyclophosphamide in severe SSc, including

73 (97%) participants with pulmonary involvement. HSCT was superior to cyclophosphamide in terms of Global Rank Composite Score (comprising in hierarchical order: death, event-free survival, FVC, Health Assessment Questionnaire-Disability Index (HAQ-DI) and mRSS) and change in FVC.<sup>112</sup> Notably, patients with severe lung disease (FVC <45% or DL<sub>CO</sub> <40% predicted) were excluded, as were those with left ventricular ejection fraction <50%, severe renal impairment, PAH or more than 6 months of previous treatment with cyclophosphamide.<sup>112</sup>

### SUMMARY

- Risk factors for severe and/or progressive SSc-ILD include greater extent of ILD on HRCT, declining PFT, Scl-70 autoantibody positivity and development of ILD early in the SSc disease course.<sup>54,55,78,79,96</sup>
- MMF has been demonstrated to stabilize SSc-ILD and is generally regarded as the initial therapy of choice when treatment is required. Azathioprine or cyclophosphamide (typically IV, given the lower cumulative toxicity) may be an alternative to MMF.<sup>102–104</sup>
- The use of concomitant corticosteroids is controversial and if prescribed, the dose should be minimized (<10–15 mg/day) to reduce side effects including the risk of SSc renal crisis.
- Nintedanib has been shown to slow lung function decline in SSc-ILD, although it is not yet approved for this indication in Australia or New Zealand.<sup>85</sup>
- HSCT may improve SSc-ILD and survival in highly selected SSc patients, although its role is likely to be limited to specialist centres.<sup>111,112</sup>

### Rheumatoid arthritis

Interstitial changes on HRCT occur in up to 40–50% of newly diagnosed RA patients, with up to 10% developing clinically significant ILD during their lifetime.<sup>18,113</sup> ILD may precede articular symptoms or appear many years after RA diagnosis. Male gender, older age at RA onset, smoking history, positive rheumatoid factor (RF) and anti-CCP antibodies are associated with increased risk of ILD.<sup>19,114,115</sup> Both RA-ILD and IPF share a number of genetic risk factors, including the *MUC5B* promoter variant, and genes associated with telomere maintenance (*TERT*, *TERC* and *TINF-2*).<sup>116,117</sup> Given the high prevalence of subclinical ILD in RA, a low threshold for respiratory investigation in patients with seropositive RA is suggested.<sup>10</sup> ILD has been reported in patients with anti-CCP antibodies without a clinical diagnosis of RA, but it is unknown what proportion progress and develop clinically apparent joint disease.<sup>81</sup>

UIP is the most common radiological and histopathological pattern in RA, followed by NSIP, OP and, rarely, acute interstitial pneumonia (AIP) or LIP.<sup>37,113</sup> RA-UIP is associated with poorer survival, with most but not all studies suggesting a prognosis similar to IPF.<sup>24,25,38</sup> Other negative prognostic factors include lower baseline PFT and declining PFT in the first 6 months.<sup>24,30,118</sup>

There are no randomized controlled trials (RCT) assessing immunosuppressive therapy specifically in RA-ILD. Case series and retrospective series report stabilization or improvements in lung function with corticosteroids, conventional immunosuppressive agents (e.g. cyclophosphamide, azathioprine and MMF) and rituximab.<sup>119–121</sup> RA-ILD with UIP may be less responsive to immunosuppressive therapy, although retrospective series have reported stabilization of pulmonary function with MMF.<sup>122</sup> Given the increased morbidity and mortality associated with immunosuppression in IPF, the decision to immunosuppress in RA-ILD requires caution.<sup>123</sup> The recently reported INBUILD study demonstrated reduced rate of decline in FVC in a mixed cohort of patients with progressive fibrosing ILD, including 89 patients with RA-ILD.<sup>86,87</sup> As of July 2020, a multicentre trial of pirfenidone in RA-ILD (NCT02808871) is ongoing.

In patients with established RA-ILD, the safety of MTX and other potentially pneumotoxic disease-modifying antirheumatic drugs remains under debate.<sup>124,125</sup> While MTX pneumonitis is a recognized rare adverse event (estimated prevalence of 0.43% in RA patients), the impact of MTX on established RA-ILD remains uncertain.<sup>126</sup> MTX treatment was not associated with an increased risk of RA-ILD in a cohort of 2701 patients with newly diagnosed RA.<sup>127</sup> Furthermore, a case series of 78 patients with RA-ILD (two-thirds receiving MTX) reported improved survival in the MTX subgroup.<sup>128</sup> Thus, pre-existing ILD is not a specific contraindication to MTX therapy, but caution is advised in patients with limited respiratory reserve.<sup>90</sup>

Leflunomide and other biologic agents (e.g. TNF inhibitors, rituximab and tocilizumab) have all been associated with pulmonary toxicity, but it is unknown if pre-existing ILD is an independent risk factor.<sup>129–134</sup> Given these uncertainties, caution and vigilance for a decline in lung function is required if considering these agents in patients with RA-ILD.<sup>120,135</sup>

## SUMMARY

- In RA-ILD, a UIP pattern, lower baseline PFT and declining PFT are associated with a poorer prognosis.<sup>24,25,30,118</sup>
- Controlled treatment trial data for managing RA-ILD are lacking. A variety of immunosuppressive agents (including cyclophosphamide, azathioprine, MMF or rituximab) may be effective in ameliorating decline in RA-ILD.
- In the setting of progressive RA-ILD, consideration should be given to cessation of disease-modifying anti-rheumatic drugs (leflunomide and TNF inhibitors), given the potential for these agents to precipitate worsening ILD.
- Clinical trials evaluating nintedanib and pirfenidone for RA-ILD are ongoing.

## Idiopathic inflammatory myopathy

The IIM spectrum of disorders includes polymyositis (PM), DM, inclusion body myositis (IBM) and

immune-mediated necrotizing myopathy (IMNM).<sup>136</sup> ILD is a major cause of morbidity and mortality in PM/DM, with an estimated prevalence of 20–65%, including rapidly progressive ILD.<sup>137,138</sup> IBM and IMNM are not typically associated with pulmonary involvement and will not be discussed.<sup>139,140</sup>

The recently revised IIM diagnostic criteria incorporate demographic, clinical, serological and muscle biopsy features to determine the likelihood of disease (Table 1).<sup>136,140,141</sup> Pragmatically, myositis in the presence of cutaneous features (including mechanic's hands, Gottron's papules and a heliotrope rash) supports a diagnosis of DM, while positive muscle biopsy findings and elevated serum creatinine kinase (CK) in the absence of cutaneous features suggests PM. CADM is a subgroup of IIM with cutaneous findings in the absence of myositis.<sup>140,142,143</sup>

Autoantibodies are a key diagnostic feature in IIM and are broadly classified into MSA and myositis-associated autoantibodies (MAA) (Table 2). In most pathology laboratories in Australia and New Zealand, these antibodies are not included in standard ENA testing, and need to be specifically requested. Of the MSA, the presence of anti-tRNA synthetase antibody (most commonly anti-Jo1) is a defining feature of the anti-synthetase syndrome and highly associated with ILD (prevalence up to 71%).<sup>137,140</sup> While the anti-MDA5 antibody may be associated with CADM and rapidly progressive ILD (particularly in individuals of Asian ethnicity), it may also be associated with a more benign clinical course.<sup>84,141–143</sup> Specific IIM phenotypes are associated with an increased risk of malignancy, especially lung, breast, colorectal and pancreas and targeted screening may be appropriate. Positive anti-TIF1 $\gamma$  and anti-nuclear matrix protein (NXP)-2 antibodies in particular have a reported 27- and 3.68-fold higher risk of malignancy, respectively, among DM patients.<sup>144</sup>

Subclinical ILD appears to be less common in IIM compared with other CTD, with the majority of IIM-ILD patients tending to have more severe, progressive lung involvement requiring treatment. In the absence of randomized controlled data, several treatment recommendations have been proposed by expert groups. Oral prednisolone (0.25–1 mg/kg) for 3–8 weeks followed by slow wean has been reported to result in clinical improvement in 90–100% of patients.<sup>11,140,145</sup> Treatment of rapidly progressive IIM-ILD includes pulse IV methylprednisolone or IV cyclophosphamide, followed by steroid-sparing oral agents.<sup>145,146</sup> Azathioprine, MMF, calcineurin inhibitors (cyclosporine and tacrolimus) and rituximab have all demonstrated benefit in case series with small patient numbers.<sup>145,147–150</sup> A recent retrospective study of 110 IIM-ILD patients treated with azathioprine ( $n = 66$ ) or MMF reported similar improvements in PFT and reduced prednisolone requirements, although a higher frequency of adverse events were observed in the azathioprine group.<sup>148</sup> IV immunoglobulin (IVIG) is beneficial in active muscle disease, although efficacy for ILD specifically remains unclear.<sup>151</sup> Plasmapheresis is generally reserved for severe multiorgan disease, although evidence for its role specifically in IIM-ILD is limited.<sup>152–154</sup> Due to the risk of worsening or relapsed

ILD, immunosuppression is generally maintained for a relatively long duration (often >2–5 years), although controlled treatment data are lacking. Despite treatment, morbidity and mortality related to IIM-ILD are significant, with 25% of patients deteriorating despite treatment and an overall ILD-associated mortality rate of 13.5% at 5 years in one case series.<sup>146</sup>

### SUMMARY

- ILD is a major contributor to IIM mortality and warrants expedited evaluation and treatment.<sup>137,138</sup>
- Initial intensive immunosuppression with high-dose corticosteroids (oral or IV), IV cyclophosphamide or rituximab is often required to achieve control in progressive IIM-ILD. IVIG and plasmapheresis may play a role in the acute setting.<sup>145,147,151,152,154</sup>
- Maintenance immunosuppression with low-dose corticosteroids and steroid-sparing agents (including MMF, azathioprine and calcineurin inhibitors) is generally required following initial high-dose therapy, without evidence of an obviously superior agent.<sup>146–149</sup>

### Other CTD

#### *Systemic lupus erythematosus*

Clinically significant pulmonary complications involving the interstitium, pulmonary vasculature and/or pleura occur in 3–8% of SLE patients.<sup>155</sup> ILD is uncommon, but in rare cases, heralded by life-threatening acute lupus pneumonitis and diffuse alveolar haemorrhage. Whilst elevated erythrocyte sedimentation rate (ESR) and/or hypocomplementaemia are indicators of systemic SLE disease activity, the presence of autoantibodies (e.g. ANA and anti-dsDNA) do not correlate with the risk of ILD.<sup>156–158</sup>

Pleural disease is the most common pulmonary manifestation, with pleurisy and/or pleural effusion occurring in over 60% of patients.<sup>159</sup> Shrinking lung syndrome is a rare, poorly understood complication of SLE, characterized by pleuritic chest pain, restrictive physiology and no interstitial changes on imaging.<sup>5</sup> Other pulmonary manifestations of SLE include PH and thromboembolic disease, especially in association with antiphospholipid syndrome.<sup>160,161</sup>

#### *Sjögren's syndrome*

Clinically significant ILD is rare in Sjögren's syndrome (SjS), and most commonly follows a mild, self-limited disease course.<sup>155,162</sup> SjS-associated ILD (SjS-ILD) is typically more female predominant, with a median age of onset of 60 years and occurring 5–10 years after SjS diagnosis.<sup>134</sup> Autoantibodies do not predict risk of SjS-ILD, although presence of anti-Ro/SS-A autoantibodies correlated with a lower DL<sub>CO</sub> in one case series.<sup>163</sup> LIP was previously considered the most common radiological pattern in SjS, but recent reports suggest NSIP predominates.<sup>39</sup> It is important to distinguish dry mucous

membranes (xerotrachea) as a cause or contributor to symptoms, especially dry cough, independent of ILD.<sup>155</sup>

SjS patients are at increased risk for lymphoma, especially mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>155,164</sup> Pulmonary lymphoma occurs in 1–2% of patients with primary SjS, and accounts for approximately 20% of all SjS-associated lymphoma.<sup>165</sup> It is important to distinguish pulmonary lymphoma from LIP. Both can manifest with ground-glass opacification, cysts, parenchymal nodules and lymphadenopathy.<sup>158</sup> Other rare pulmonary complications in SjS include pleuritis, vascular disease (PAH and pulmonary embolism), amyloidosis, 'shrinking lung' and 'middle lobe' syndromes.<sup>158,166–169</sup>

#### *Undifferentiated and mixed connective tissue disease*

Undifferentiated CTD (UCTD) is a term used to describe the early, 'undifferentiated' phase of a CTD with clinical symptoms and signs of a CTD and non-specific laboratory abnormalities (e.g. ANA and ENA), not satisfying diagnostic criteria for a defined CTD. UCTD does not have a well-accepted definition and is broadly encompassed within the IPAF definition (discussed later).<sup>170</sup> Approximately one-third of UCTD patients progress to a definable CTD over 5-year follow-up.<sup>171</sup>

MCTD has a distinct clinical phenotype and human leukocyte antigen (HLA) profile, although controversy remains with four available diagnostic criteria.<sup>17,172,173</sup> The central concept of MCTD is an overlap syndrome associated with anti-U1 ribonucleoprotein (anti-RNP) antibodies.<sup>174</sup> Peak incidence is around the age of 40 years.<sup>174</sup> Clinical features always include Raynaud's phenomenon and at least two of: myositis, arthritis, oesophageal dysmotility, leucopaenia, serositis and ILD or PAH.<sup>174</sup> Diagnosis is challenging due to the overlap of clinical features with other CTD and requires continual reassessment.

HRCT abnormalities occur in approximately half of MCTD patients, with one-third demonstrating ILD.<sup>175</sup> Anti-Ro52 antibodies are a potential marker of lung involvement.<sup>175</sup> MCTD-ILD is severe in approximately one-fifth of patients, and associated with a 21% mortality compared with 3% in patients with a normal HRCT.<sup>175</sup>

#### *Treatment of SLE, SjS, UCTD and MCTD-ILD*

The optimal therapy for ILD associated with SLE, SS, UCTD and MCTD is unknown due to a lack of controlled treatment trials. In clinical practice, broad CTD-ILD treatment principles remain pertinent with therapeutic intervention based on ILD severity and rate of progression, other organ involvement and comorbidities. Extrapolating from treatment trials in other CTD, mild, non-progressive ILD may be monitored, whilst treatment with immunosuppression (e.g. corticosteroids, azathioprine and MMF) is reasonable where there is evidence of progression. Treatment trials on the utility of rituximab in these CTD are ongoing.<sup>176</sup>



**Table 6** ERS/ATS criteria for the diagnosis of IPAF

| Domain            | Characteristics  |
|-------------------|--|
| (A) Clinical      | Distal digital fissuring (i.e. 'mechanic's hands')<br>Distal digital tip ulceration<br>Inflammatory arthritis or polyarticular morning joint stiffness $\geq 60$ min<br>Palmar telangiectasia<br>Raynaud's phenomenon<br>Unexplained digital oedema<br>Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)  |
| (B) Serological   | ANA $\geq 1:320$ titre, diffuse, speckled, homogeneous patterns or ANA nucleolar pattern (any titre) or ANA centromere pattern (any titre)<br>RF $\geq 2 \times$ ULN<br>Anti-CCP<br>Anti-dsDNA<br>Anti-Ro (SS-A)<br>Anti-La (SS-B)<br>Anti-ribonucleoprotein<br>Anti-Smith<br>Anti-topoisomerase (Scl-70)<br>Anti-tRNA synthetase (e.g. Jo-1, PL-7, PL-12, others are: EJ, OJ, KS, Zo, YRS)<br>Anti-PM-Scl<br>Anti-CADM (MDA5)   |
| (C) Morphological | (1) Suggestive radiology patterns by HRCT<br>NSIP<br>OP<br>NSIP with OP overlap<br>LIP<br>(2) Histopathology patterns or features by surgical lung biopsy<br>NSIP<br>OP<br>NSIP with OP overlap<br>LIP<br>Interstitial lymphoid aggregates with germinal centres<br>Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)<br>(3) Multi-compartment involvement (not otherwise explained)<br>Pleural effusion or thickening<br>Pericardial effusion or thickening<br>Small airways disease (by PFT, imaging or pathology)<br>Pulmonary vasculopathy |

Adapted from Fischer *et al.*,<sup>180</sup> with permission.

ANA, anti-nuclear antibody; ATS, American Thoracic Society; CADM, clinically amyopathic dermatomyositis; CCP, cyclic citrullinated peptide; dsDNA, double-stranded DNA; ERS, European Respiratory Society; HRCT, high-resolution computed tomography; IPAF, interstitial pneumonia with autoimmune feature; LIP, lymphocytic interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PFT, pulmonary function test; PM, polymyositis; RF, rheumatoid factor; ULN, upper limit of normal.

## SUMMARY

- ILD is a recognized complication in SLE, SjS, UCTD and MCTD but is typically less frequent than the other CTD.
- Limited data exist to guide treatment decisions in this group with therapeutic approaches generally extrapolated from other CTD.
- In severe and/or progressive ILD, high-dose corticosteroids in combination with a steroid-sparing agent (MMF or azathioprine) is a reasonable initial treatment approach.
- Several unique pulmonary complications may occur in SjS (lymphoma and amyloidosis) and SLE (lupus pneumonitis and pulmonary haemorrhage), requiring a high degree of diagnostic suspicion to enable timely diagnosis.

## Interstitial pneumonia with autoimmune features

While ILD can develop in the context of a known CTD, it is increasingly recognized that some patients with idiopathic ILD have features of autoimmune disease, but do not fulfil criteria for a defined CTD. Historically, various terms including 'UCTD-associated ILD', 'lung-dominant CTD' or 'autoimmune-featured ILD' have been used to describe such patients, impeding uniform study of this important cohort.<sup>177-179</sup> In 2015, a ERS/ATS Taskforce defined this group as 'IPAF'.<sup>180</sup> The proposed classification criteria remain a research framework rather than clinical classification, requiring revision and validation in future studies.

The full criteria consist of three domains—clinical, serological and morphological (Table 6). Qualifying individuals must demonstrate characteristics from at least two of the three domains. Serological evaluation includes a broad array of autoantibodies including an extended ENA and myositis panel, high titre ANA and RF level.<sup>180</sup> Multi-compartment involvement in the morphological domain includes ILD with unexplained pleuro-pericardial involvement, pulmonary vasculopathy or airways disease.

Since publication of the IPAF classification criteria, several retrospective single-centre studies have described IPAF populations with heterogeneous demographics, clinical features and natural history.<sup>181</sup> One landmark study demonstrated no difference in survival between IPAF and IPF patients, although there was a clear demarcation in survival between those with and without a UIP pattern on HRCT.<sup>182</sup> However, other studies have not replicated this finding and larger multicentre, prospective studies are needed.<sup>183</sup>

Little is known about the best clinical approach to managing patients who meet the IPAF research criteria. Indeed, IPAF is likely to be comprised of a heterogeneous group of patients, in which different therapies are targeted at different patient phenotypes. At present, a pragmatic approach would be to consider the underlying ILD diagnosis by ILD-MDM and treat the patient accordingly. In patients who are considered to have

CTD-ILD, treatment will usually follow an approach similar to SSc-ILD, whereas, in patients considered to have IPF, anti-fibrotic therapy may be appropriate. The recently published pirfenidone in unclassifiable ILD study included 33 (13%) patients with IPAF, too small a number to make meaningful conclusions.<sup>88</sup> Ongoing studies in this patient population are required.

### SUMMARY

- IPAF identifies a heterogeneous patient group with ILD and features suggestive of a CTD, not meeting established classification criteria for a specific CTD.<sup>180</sup>
- It remains a research framework rather than clinical diagnosis.
- There is no current consensus for the management of patients meeting IPAF criteria, with several ongoing studies evaluating the role of immunosuppressive and antifibrotic therapies

### Vasculitis and ILD

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), incorporating granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA) may affect the lung parenchyma, blood vessels and airways. While diffuse alveolar haemorrhage and parenchymal mass lesions (with or without cavitation) are the most frequent pulmonary manifestations of AAV, ILD is an increasingly recognized complication, particularly in MPA where there is an estimated prevalence of 7–36% and significant associated morbidity.<sup>184–186</sup>

Positive ANCA serology has been reported in 4–10% of patients with a confirmed diagnosis of IPF.<sup>184,187,188</sup> However, the significance of myeloperoxidase (MPO) or proteinase 3 (PR3) antibodies remains uncertain, with inconsistent clinical and radiological findings reported in several small single-centre studies.<sup>184,186–190</sup> Recently, a large retrospective cohort of 745 IPF patients from two North American expert ILD centres identified ANCA in 34 (4.6%) patients at the time of IPF diagnosis.<sup>191</sup> Of the ANCA-positive patients, 18 (53%) were MPO-antibody positive, 10 PR3-antibody positive (29%) and 6 (18%) with non-specific ANCA positivity.<sup>191</sup> ANCA positivity was not associated with baseline IPF severity or transplant-free survival. During follow-up (median: <18 months), 28% of MPO-positive patients developed clinically significant vasculitis, most commonly renal disease and mononeuritis multiplex. No PR3-positive or non-specific ANCA patients developed clinical vasculitis.<sup>191</sup>

Treatment for systemic vasculitis usually involves guideline-recommended immunosuppressive regimens, but data specific to AAV-associated ILD (AAV-ILD) are limited.<sup>187,192</sup> Some case series suggest clinical or radiological improvement with immunosuppressive therapy, but impact on overall survival and progression of lung disease remains controversial and further research is required.<sup>184,186–188,193</sup> Generally speaking, ILD occurring in the context of positive ANCA serology

without clinical evidence of vasculitis should be treated on its merits, based on the principles discussed in section 'Approach to management of CTD-ILD'.<sup>194,195</sup>

### SUMMARY

- The association between AAV and ILD, particularly IPF, is increasingly recognized, although variable clinical manifestations have been reported in published series.<sup>184–186</sup>
- Positive MPO serology appears to be more strongly linked to the development of systemic vasculitis.<sup>191</sup>
- Optimal treatment, including the use of immunosuppressive therapy, remains the focus of ongoing research.

### Psoriasis and ILD

There are small retrospective case reports and case series of ILD in patients with psoriasis and psoriatic arthritis, although a clear pathogenic association is yet to be determined. Observed radiological patterns on HRCT include UIP, NSIP and OP with descriptions of non-specific bilateral lower zone predominant ground-glass opacities with irregular reticular changes.<sup>196–200</sup> Most reported cases are mild with minimal or no respiratory symptoms.<sup>196,197</sup> Correlation between dermatological and pulmonary disease activity, and response of pulmonary disease to immunosuppressive treatment for the skin, is also variable.<sup>196–198</sup> Small case numbers limit meaningful conclusions and further prospective studies are required to determine if a clear association with ILD exists, and to clarify prevalence and pathogenic mechanisms. Careful observation for pulmonary complications in patients with psoriasis, as with any systemic inflammatory disease, is reasonable.

### SPECIAL CONSIDERATIONS IN CTD-ILD MANAGEMENT

#### CTD-ILD with pulmonary hypertension

PH is defined as a mean pulmonary artery pressure of  $\geq 25$  mm Hg at rest on right heart catheterization (RHC), although a revised threshold of  $>20$  mm Hg in combination with a pulmonary vascular resistance of  $\geq 3$  Wood Units has recently been proposed.<sup>201</sup> Clinical conditions associated with PH are classified into five groups based on similar pathophysiological mechanisms, characteristics and management, as outlined in the updated World Health Organization (WHO) World Symposium on Pulmonary Hypertension classification.<sup>201</sup> In CTD-ILD, it is important to ascertain whether PH is a primary vasculopathy (i.e. PAH 'CTD-PAH'; WHO Group 1 PAH) or secondary to the underlying CTD-associated ILD ('CTD-ILD-PH'; WHO Group 3 PH). Furthermore, PH secondary to left heart disease (WHO Group 2 PH) may also be present, further complicating classification of these patients. The presence of PH regardless of cause is a poor prognostic marker. The ASPIRE Registry estimated a 5-year survival of 25%

for SSc-associated PAH and 30% for PH secondary to lung disease.<sup>202</sup> A recent study demonstrated similarly dismal prognosis in patients with severe ILD and mild-moderate PH, and severe PAH with minor ILD, with 3-year survival rates of 49.9% and 61.9%, respectively.<sup>203</sup>

Clues suggest that PH may include breathlessness out of proportion to lung function or radiological severity, features of right heart failure (e.g. syncope, presyncope or fluid retention) or it may be detected on screening echocardiogram (as recommended in patients with SSc). Differentiating Group 1 PAH from Group 3 PH in CTD-ILD patients is often complex and requires careful evaluation at an experienced PH centre. Ancillary investigations suggesting Group 3 PH include an FVC <70% predicted, extensive interstitial changes on HRCT and exhausted ventilatory reserve on cardiopulmonary exercise testing (e.g. reduced breathing reserve, normal O<sub>2</sub> pulse, normal CO/VO<sub>2</sub> slope and an increase in PaCO<sub>2</sub> during exercise).<sup>204</sup> Ultimately, expert clinical judgement is often required for accurate diagnosis. The presence of mild ILD does not preclude the presence of concomitant Group 1 PAH, and major clinical trials evaluating PAH-specific therapies permitted mild impairments in lung function.

In Group 1 PAH, pulmonary vasodilator therapies have proven therapeutic benefit.<sup>205–208</sup> SSc is the dominant CTD associated with PAH (estimated prevalence of 8–12%), but PAH can also occur in RA, SLE and MCTD.<sup>209</sup> PAH-specific therapies include endothelin receptor antagonists, phosphodiesterase (PDE5) inhibitors, the cyclic GMP stimulator riociguat and prostacyclin analogues. The European Society of Cardiology(ESC)/ERS guidelines advocate a ‘treat to target’ approach using combination PAH-drug therapy, with commencement of therapy in those with WHO Functional Class II symptoms.<sup>210</sup> Current regulatory restrictions in Australia and New Zealand only fund one agent at a time for patients with WHO Functional Class II or above symptoms.

Conversely, PAH-specific therapies are generally not beneficial in Group 3 PH, with potential for worsening ventilation/perfusion (V/Q) mismatch and consequent hypoxaemia. Management should focus on treating the ILD and hypoxaemia. Evidence-based guidelines for the management of PH coexisting with moderate-to-severe CTD-ILD do not currently exist.

General management of all CTD patients with PH includes diuresis, supervised exercised programmes and domiciliary oxygen as required. As for all PH, there is no clear evidence for anticoagulation (in the absence of another indication), pregnancy should be avoided and anaesthesia carries significant additional risks.

## SUMMARY

- Elevated pulmonary pressure in the setting of CTD carries a significant negative prognostic impact and warrants evaluation at an experienced PH centre.
- In CTD-PAH (WHO Group 1), pulmonary vasodilator therapies are beneficial and should be

instituted once a PAH diagnosis is confirmed, ideally at WHO functional class II level.<sup>206–208,210</sup>

- Treatment escalation of CTD-PAH with combination therapy as per the ESC/ERS guidelines is recommended.<sup>210</sup>
- PH complicating CTD-ILD (WHO Group 3) should prompt optimization of ILD therapy and correction of hypoxaemia.

## Lung transplantation for CTD

Approximately 9–12% of CTD-ILD patients progress to end-stage respiratory failure, despite appropriate immunosuppressive therapy and lung transplantation are potential treatment options. CTD is not a relative or absolute contraindication to transplantation, yet less than 2% of all lung transplants worldwide between 1995 and 2010 were for patients with CTD-associated lung disease.<sup>211–213</sup> Factors complicating transplant management and outcomes in CTD include immune dysregulation, GORD, renal disease and active myositis. Oesophageal dysfunction is common in CTD patients, especially in those with SSc, and GORD is potentially associated with the development of chronic lung allograft dysfunction and post-transplant morbidity and mortality.<sup>214</sup> The presence of untreatable significant dysfunction of another major organ system (e.g. heart, liver, kidney or brain) is an absolute contraindication unless combined organ transplantation can be performed.<sup>213</sup>

Recent studies suggest that carefully selected CTD patients with pulmonary disease warrant transplantation assessment, with similar post-transplant outcomes to other cohorts. Evaluation of 284 lung transplantations in CTD patients from 1991 to 2009 included in the United States Organ Procurement and Transplantation Network database reported that there were no post-transplant recurrences of CTD lung disease, extrapulmonary flares of the CTD were rare (one possible flare per 20.3 patient years) and cumulative survival was similar to IPF patients.<sup>215</sup>

This was echoed by a single-centre cohort study of 892 lung transplant recipients, including 72 with SSc-ILD and 311 with pulmonary fibrosis from other causes (other ILD).<sup>216</sup> SSc-ILD recipients demonstrated satisfactory short-term survival (100% 30-day and 80.6% 1-year survival) and no difference in 5-year survival (conditional on 1-year survival) compared to other ILD (66% vs 58%, respectively,  $P = 0.249$ ).<sup>216</sup> Importantly, SSc-ILD recipients also had superior bronchiolitis obliterans syndrome (BOS)-free survival.<sup>216</sup> Careful evaluation with 24 h pH monitoring and oesophageal manometry (before and/or early after transplant) may aid reflux management, including planning laparoscopic fundoplication post-transplant as a strategy for long-term allograft protection.

Case series of successful transplant outcomes are emerging for myositis patients, but the presence of active myositis requiring immunosuppression pre-transplant, especially steroids, may complicate post-transplant management, rehabilitation and outcomes.<sup>217</sup>

## SUMMARY

- In selected CTD-ILD patients, survival following lung transplantation is comparable to non-CTD patients with similar restrictive lung disease.<sup>215</sup>
- Given the unique challenges in CTD-ILD, early assessment by an experienced transplant physician should be undertaken in those patients with severe and/or progressive lung disease who may be suitable transplant recipients.

## Non-pharmacological management in CTD-ILD

People with CTD-ILD often experience dyspnoea, fatigue, anxiety, depression, cough and reduced exercise tolerance.<sup>155,218</sup> These symptoms are debilitating and substantially affect HRQoL.<sup>219,220</sup> The CTD are further complicated by other systemic manifestations including arthropathy, vasculopathy, exercise-induced hypoxaemia and corticosteroid-induced myopathies which may further impair exercise tolerance. Non-pharmacological strategies such as pulmonary rehabilitation (PR), supplemental oxygen and the early integration of palliative care can positively impact symptoms and HRQoL in this population.

### Pulmonary rehabilitation

There is increasing evidence that PR is effective at improving exercise tolerance, dyspnoea and HRQoL in ILD.<sup>221–223</sup> Whilst there are no RCT of PR in CTD-ILD specifically, one study including patients with CTD-ILD found clinically meaningful benefits in HRQoL in subgroup analysis, despite limited improvements in exercise capacity. PR is strongly recommended in the British Thoracic Society PR guidelines for all patients functionally limited by dyspnoea.<sup>222,224</sup> It is possible that musculoskeletal limitations (joint pain, swelling and stiffness) may limit the gains in exercise capacity that can be achieved with traditional PR. Alternative strategies could include water-based training, which is effective in COPD patients with physical comorbidities.<sup>225</sup> PR also incorporates education, nutrition counselling and psychological support, which may assist to improve emotional and physical well-being in this population.<sup>226,227</sup>

### Supplemental oxygen

Clinical practice guidelines provide strong recommendations for the use of long-term oxygen therapy (LTOT ≥18 h per day) for people with ILD who have resting hypoxaemia.<sup>228,229</sup> This is based on studies in COPD where it is known to improve survival. Supplemental oxygen may provide symptomatic relief in patient with advanced ILD.<sup>230,231</sup> The role of oxygen therapy in people with ILD who have exertional desaturation without resting hypoxaemia is less clear. Two small studies in IPF found that oxygen significantly increased endurance time and reduced exertional dyspnoea during constant load cycling.<sup>232,233</sup> This supports the ATS/ERS

PR guidelines recommendation for supplemental oxygen during exercise training in patients who desaturate on exertion.<sup>226</sup> A recent crossover trial of short-term (2 weeks) use of ambulatory oxygen in fibrotic ILD demonstrated a significant improvement in HRQoL.<sup>234</sup> Longer term outcomes remain unclear. There are two current RCT including a comparison of the effects of ambulatory oxygen with room air over 3 months (NCT02286063 and NCT02551068) and the benefits of oxygen during an 8-week exercise programme (NCT02551068).

### Symptom management and palliative care

Palliative care aims to alleviate symptom burden, especially dyspnoea and cough, address advance care planning and optimize HRQoL throughout the disease course.<sup>231,235</sup> Palliative care should occur in parallel with all other treatments and not be delayed until the disease is advanced.<sup>231,236</sup> As discussed, supplemental oxygen and PR play an important role in self-management and reducing dyspnoea.<sup>221</sup> Opioids, up to a dose of 30 mg morphine daily, might safely relieve dyspnoea.<sup>3,230,231,237,238</sup> Evidence for the use of benzodiazepines is limited, but may be an alternative in those with dyspnoea associated with anxiety or not controlled by opioids.<sup>231,235,238,239</sup> Caution is required with both opioids and low-dose benzodiazepines associated with increased hospital admissions and mortality in patients with oxygen-dependent ILD.<sup>240</sup>

Treatment of cough is difficult and requires investigation for, and treatment of, GORD given its high prevalence in CTD-ILD.<sup>236,241</sup> Thalidomide has been shown to reduce cough in IPF, although there is no evidence of its effect in CTD-ILD.<sup>231,241</sup> Gabapentin appears effective for refractory chronic cough and mucolytic agents may be useful in assisting with sputum clearance, but CTD-ILD specific data are lacking.<sup>242,243</sup> Low-dose opiates may be considered to palliate cough when alternative treatments have been unsuccessful.<sup>238,241,244</sup>

Non-pharmacological interventions such as hand-held fans, rollator devices, breathing exercises and speech pathology may also prove beneficial in relieving symptoms.<sup>231,238,244,245</sup> Symptom management should also address depression, anxiety, fatigue and deconditioning, for which PR and psychotherapy may be of assistance.<sup>227,231,238,246–249</sup> Education, support and assistance for self-management for both patients and caregivers is important in optimizing quality of life and in advanced care planning. Timely patient-centred end-of-life care should be offered to all patients where progressive disease is evident or expected.<sup>231</sup>

## SUMMARY

- In CTD-ILD, PR can help improve exercise tolerance, dyspnoea and HRQoL.
- LTOT should be offered in those patients with resting hypoxaemia. Supplemental oxygen during exercise training in those with exertional desaturation may facilitate PR outcomes.<sup>221,229,233,234,236</sup>

- Palliative care should be considered in parallel with other treatment interventions to optimize symptom management.<sup>235</sup>

## FUTURE DIRECTIONS

The next 5 years will see the most significant changes in the available therapies and the evidence base supporting treatment choice for CTD-ILD. Some of the most important treatment trials in CTD-ILD are listed in Table 5. Anti-fibrotics additional to immunosuppression are an active area of current research. As discussed, the SENSIS study demonstrated efficacy of nintedanib in SSc-ILD, and long-term safety is being evaluated in an open-label extension study (NCT03313180).<sup>176</sup> The utility of pirfenidone in combination with MMF for SSc-ILD is being assessed in the Scleroderma Lung Study III (NCT03221257) and the TRAIL1 study is evaluating pirfenidone in RA-ILD (NCT02808871).

Rituximab is generally reserved for severe CTD-ILD progressing despite conventional therapy. However, rituximab as 'induction' therapy (1 g at baseline and 2 weeks) is being evaluated in two ongoing clinical trials—one comparing rituximab with placebo and background MMF therapy in both arms in a broad range of CTD-ILD (NCT02990286), and a second comparing rituximab with IV cyclophosphamide (600 mg/m<sup>2</sup> 4 weekly for six doses) in SSc-ILD, IIM and MCTD (NCT01862926).<sup>176</sup> As discussed, tocilizumab was recently found to be associated with stabilization of FVC in SSc with final analysis awaited.<sup>109</sup>

Genetic studies in CTD-ILD are only just being reported, but it seems likely that there will be increasing recognition of gene-environment interactions and their impact on disease pathogenesis and prognosis, similar to IPF and chronic hypersensitivity pneumonitis.<sup>116,250</sup> The incorporation of genomic markers to aid in diagnosis, risk stratification and clinical decision-making together with the identification of other molecular biomarkers may be of particular importance in CTD-ILD, given the characteristically variable disease course.<sup>251</sup>

The rarity of CTD-ILD in general will continue to present difficulties obtaining evidence and reimbursement for therapeutic agents, especially for orphan CTD-ILD (e.g. SjS-ILD and anti-synthetase syndrome). However, advances in diagnostic and therapeutic modalities, and the evidence base that underpins their place in clinical practice, will significantly improve both the safety and efficacy of care for all patients with CTD-ILD.

## SUMMARY AND CONCLUSIONS

Management of CTD-ILD is a challenging endeavour, requiring a multidisciplinary approach in order to achieve the best possible outcomes for patients and their caregivers. Accurate diagnosis, staging of severity and monitoring progression of CTD-ILD require the at times complicated integration of clinical, radiological,

physiological and serologic data, often with substantial input from non-respiratory specialists. While immunosuppression remains the mainstay of treatment for severe and/or progressive CTD-ILD, deciding when to start therapy, which agent to use and duration of therapy is a nuanced decision impacted by many clinical and patient specific factors. An ever-expanding array of treatment options, including monoclonal antibodies targeting specific molecular pathways and the anti-fibrotic agents, are being evaluated with promising early results and are providing new insights into disease pathophysiology.

In this position statement, we have endeavoured to provide both an overview of general principles of CTD-ILD monitoring and treatment in addition to disease-specific guidance. However, it is important to note that given the heterogeneous clinical course of many CTD-ILD, no single management strategy will capture every clinical scenario, and continued assessment and calibration of treatment approach is vital. Given the rarity of some of the CTD-ILD and absence of specific treatment evidence, by necessity therapeutic approaches are often extrapolated from other CTD-ILD with assumed similar disease mechanisms. This paucity of treatment evidence represents a major unmet clinical need across many CTD-ILD, and should remain a priority for future research. Finally, non-pharmacological therapies are a key and often overlooked aspect in the holistic care of patients with these multi-system disorders.

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**Abbreviations:** AAV, ANCA-associated vasculitis; Ab, antibody; AE, adverse event; AIP, acute interstitial pneumonia; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; ASSIST, American Scleroderma Stem Cell versus Immune Suppression Trial; ASTIS, autologous stem cell transplantation; ATS, American Thoracic Society; AZA, azathioprine; BAL, bronchoalveolar lavage; BP, blood pressure; CADM, clinically amyopathic DM; CCP, cyclic citrullinated peptide; COPD, chronic

obstructive pulmonary disease; CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; CTD, connective tissue disease; CTD-ILD, CTD-associated ILD; CYC, cyclophosphamide; DAD, diffuse alveolar damage; DL<sub>CO</sub>, diffusing capacity for carbon monoxide; DM, dermatomyositis; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen; ERS, European Respiratory Society; ESC, European Society of Cardiology; EUC, electrolyte and urea concentration; FB, follicular bronchiolitis; FBC, full blood count; f/u, follow-up; FVC, forced vital capacity; GAP, gender, age and pulmonary function tests; GI, gastrointestinal; GORD, gastro-oesophageal reflux disease; GPA, granulomatosis with polyangiitis; HBV, hepatitis B virus; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplant; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; IIM-ILD, IIM-associated ILD; IL, interleukin; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; INBUILD, Nintedanib in Progressive Fibrosing Lung Disease; IPAF, interstitial pneumonia with autoimmune feature; IPF, idiopathic pulmonary fibrosis; IVIG, IV immunoglobulin; LFT, liver function test; LIP, lymphocytic interstitial pneumonia; LTBI, latent TB infection; LTOT, long-term oxygen therapy; MALT, mucosa-associated lymphoid tissue; MCTD, mixed CTD; MCTD-ILD, MCTD-associated ILD; MDM, multidisciplinary meeting; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MPO, myeloperoxidase; mRSS, modified Rodnan skin score; MSA, myositis-specific autoantibody; MTX, methotrexate; NSIP, non-specific interstitial pneumonia; NXP, nuclear matrix protein; OP, organizing pneumonia; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; PH, pulmonary hypertension; PJP, *Pneumocystis jirovecii* pneumonia; PM, polymyositis; PR, pulmonary rehabilitation; PR3, proteinase 3; RA, rheumatoid arthritis; RA-ILD, RA-associated ILD; RCT, randomized controlled trial; RF, rheumatoid factor; RNP, ribonucleoprotein; SAE, serious AE; SCOT, Scleroderma: Cyclophosphamide or Transplant trial; SENSISCIS, Safety and Efficacy of Nintedanib in Systemic Sclerosis; SjS, Sjögren's syndrome; SjS-ILD, SjS-associated ILD; SLE, systemic lupus erythematosus; SLS, Scleroderma Lung Study; SSc, systemic sclerosis; SSc-ILD, SSc-associated ILD; TB, tuberculosis; TPMT, test for thiopurine methyltransferase; TSANZ, Thoracic Society of Australia and New Zealand; UCTD, undifferentiated CTD; UIP, usual interstitial pneumonia; VATS, video-assisted thoracoscopic surgery; WHO, World Health Organization

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