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INTERSTITIAL LUNG DISEASE (S DHOORIA, SECTION EDITOR)

Management of Connective Tissue Disease–related Interstitial Lung Disease

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Abstract

Purpose of Review This review aims to collate current evidence on the screening, diagnosis, and treatment of various connective tissue disease (CTD)–associated interstitial lung diseases (CTD-ILD) and present a contemporary framework for the management of such patients. It also seeks to summarize treatment outcomes including efficacy and safety of immunosuppressants, anti-fibrotics, and stem cell transplantation in CTD-ILD.

Recent Findings Screening for ILD has been augmented by the use of artificial intelligence, ultra-low dose computerized tomography (CT) of the chest, and the use of chest ultrasound. Serum biomarkers have not found their way into clinical practice as yet. Identifying patients who need treatment and choosing the appropriate therapy is important to minimize the risk of therapy-related toxicity. The first-line drugs for systemic sclerosis (SSc) ILD include mycophenolate and cyclophosphamide. Nintedanib, an anti-fibrotic tyrosine kinase inhibitor, is approved for use in SSc-ILD. The US Food and Drug Administration (FDA) has recently approved tocilizumab subcutaneous injection for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD. Autologous stem cell transplantation may have a role in select cases of SSc-ILD.

Summary CTD-ILD is a challenging area with diverse entities and variable outcomes. High-resolution CT is the investigative modality of choice. Treatment decisions need to be individualized and are based on patient symptoms, lung function, radiologic abnormalities, and the risk of disease progression. Precision medicine may play an important role in determining the optimal therapy for an individual patient in the future.

Keywords Lung fibrosis · Connective tissue disease · Interstitial pneumonia with autoimmune features · CTD-ILD · Treatment

Introduction

Interstitial lung disease (ILD) occurring in a person with a known or classifiable connective tissue disease (CTD) is termed CTD-ILD. Approximately 15% of ILDs will have a background CTD [1]. Very often presence of ILD is the major determinant of mortality in a patient with a CTD [2••]. In systemic sclerosis (SSc), around 30% have symptomatic ILD and this is associated with 10-year mortality of 40% [3, 4]. For rheumatoid arthritis, severe interstitial lung disease is often reported in 2–8% while active case finding estimates are around 8–80% [5–7••]. In mixed connective tissue disease (MCTD), around 50% have ILD on CT imaging [8]. Again, in idiopathic inflammatory myositis (IIM) cohorts, there is a wide variation in the prevalence of ILD from 20 to 78% depending on the methods used to define ILD [9].

At times, a patient may have an ILD with some features of CTDs such as Raynaud or ANA (anti-nuclear antibody) positivity but not meet the criteria for any CTD. Previously, different names have been proposed for such entities such as lung dominant CTD [10]. However, with the description of the criteria for interstitial pneumonia with autoimmune

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features (IPAF), this term is now widely used in the literature [11••].

The emergence of the concept of IPAF stems from the recognition that the presence of autoimmune features predicts response to treatment, and hence, favourable prognosis [12]. Thus, clinical significance is attached to the differentiation of CTD-ILD and IPAF from idiopathic pulmonary fibrosis (IPF). IPF to CTD-ILD appears to be a continuous spectrum bridged by IPAF [13]. The component of autoimmunity is most prominent CTD-ILD, lesser in IPAF and minimal in IPF. This implies that immunosuppressant therapies have better outcomes in CTD-ILD than in IPAF, and possibly are harmful in IPF [14].

The last decade has seen a sea change in the concept of treatment of CTD-ILD from stem cell transplantation for systemic sclerosis (SSc)–ILD to the change in the dogma of avoiding methotrexate in CTD-ILD [3, 15]. Also, of the antifibrotic agents for IPF, nintedanib has shown promise even in CTD-ILD [16••]. The precipitous arrival of the COVID-19 has shown that the presence of ILD is an additional risk factor necessitating rational use of immunosuppressants in such patients [17].

Literature Search Strategy

A literature search was made on Scopus and MEDLINE/Pubmed with search terms "connective tissue disorder" or equivalent terms, "interstitial lung disease" or equivalent terms; "interstitial pneumonia with autoimmune features" and "management" or "treatment." The search was restricted to the last 3 years. The bibliography of selected articles was also scanned for additional relevant articles. The authors have focussed on recent articles but have included older articles also if they have particular relevance to current treatment strategies as per recommendations for a biomedical review [18].

Pathogenesis

Pathogenesis of CTD-ILD

There is a central role of lung epithelial damage in the pathogenesis of CTD-ILD. Genetic factors associated with SSc-ILD include HLA-DRB1 alleles, DQB1*05, interferon regulatory factor 5 (IRF5), signal transducer and activator of transcription 4 (STAT4), CD226 (DNAX accessory molecule 1), NLR family, pyrin domain containing 1 (NLRP1), interleukin-1 receptor–associated kinase-1 (IRAK1), connective tissue growth factor (CTGF), and T-cell surface glycoprotein zeta chain (CD3ζ) or CD247 [19]. The MUC5B promoter region polymorphisms have been associated with ILD at large, and also with RA-ILD [20].

In rheumatoid lung disease, the same mucosal pathological factors associated with precipitation of arthritis such as smoking or air pollutants and microbiota may also contribute to the genesis of bronchial epithelial injury [21]. Transforming growth factor-β (TGF-β), endothelin-1, and platelet-derived growth factor (PDGF) are major players in the pathogenesis of fibrosis in the setting of SSc. These lead to an endothelial mesenchymal transition (EMT) of the epithelial cell that predisposes to fibroblasts converting to myofibroblasts and leading to fibrosis [22]. The role of autoantibodies has been proposed but not fully established [23].

Knowledge of Pathogenesis Helps in Management

Elucidating the pathogenesis enables the evolution of targeted therapies [24]. The initial trials targeting TGF-β or its receptors met with mixed success [25, 26]. This might have been due to the pleiotropic effects of TGF-β as well as various redundant canonical and non-canonical downstream pathways. However, exploring the role of interleukin-6(IL-6) has led to good results with the IL-6 receptor antagonist tocilizumab. The use of subcutaneous tocilizumab led to both improvement of the modified Rodnan skin score and stabilization of functional vital capacity (FVC) [27••]. Similarly, interleukin-17 and PD-1 (programmed cell death protein1) have a role in SSc-mediated fibrosis [28]. Since there are clinically available molecules that can target these, these might be tried in the context of future clinical trials.

Screening, Monitoring, and Diagnosis

The diagnosis of CTD-ILDs is clinico-radiologic supported by the demonstration of autoantibodies. Plain chest radiographs are insensitive. The gold standard for ILD detection is high-resolution CT (HRCT) and very early disease may be better picked up on prone imaging.

Differential Diagnosis of CTD-ILD

The differential diagnosis of CTD-ILD and most important distinguishing features are summarized in Table 1.

Role of CT

HRCT is employed for diagnosis and follow-up. All CTD-ILDs do not progress. Especially in RA-ILD, 20–60% of individuals have some "interstitial lung abnormality (ILA)" of which only 35–45% progress. Sub-pleural distributions and higher total volume of ILAs are associated with progression [29••]. Therefore, it is important to find out the

Table 1 Differential diagnosis of CTD-ILD

Time frame	Differential diagnosis	Distinguishing feature(s)
Acute (hours to days)	Infections	Usually will have patchy involvement on imaging; sputum/bronchoalveolar lavage/blood cultures/PCR positive for microbes
	Diffuse alveolar damage	Common after drug/toxin induced injury Scattered or diffuse areas of ground-glass opacity; fibrosis starts within a week
	Acute eosinophilic pneumonia	Hypersensitivity-like reaction with unknown aetiology; presents fever and acute pulmonary failure; rare condition
	Vasculitis	Systemic manifestations; purpura; renal involvement; arthritis; thrombocytosis, neutrophilic leucocytosis Blood may show ANCA/cryoglobulins/anti-GBM antibodies
	Diffuse alveolar haemorrhage	Other vasculitis features present (arthritis, purpura, renal failure) or h/o specific inciting drug
Subacute (weeks to months)	Hypersensitivity pneumonitis	Extrinsic allergic alveolitis due to different inciting events: agricultural dusts, bioaerosols, microorganisms (fungal, bacterial, or protozoal)
	Sarcoidosis	Mediastinal lymphadenopathy, ankle arthritis, eye or skin manifestations may be seen
	Chronic eosinophilic pneumonia	Idiopathic eosinophilic lung disease; characterized by nonsegmental airspace consolidations with peripheral predominance
Chronic (many months to years)	Pneumoconiosis	Occupational lung diseases — history of exposure will be present
	Amyloidosis	Other manifestations: joints, kidneys, or skin
	Other ILD/idiopathic interstitial fibrosis	Absence of CTD-ILD or IPAF defining features

radiological extent and other biomarkers of progression before treating all ILAs. Quantitative CTs have the advantage of being able to quantify progression and can detect changes even before experienced radiologists [30••].

There are concerns regarding repeating CT scans for monitoring or screening due to radiation exposure. Thus, low-dose CT for screening has been developed and validated in CTD-ILD [31]. Ultra-low dose CTs have been used for other lung diseases and with the advent of artificial intelligence (AI) in radiology, it may become viable for CTD-ILD too [32]. Current quantitative CT (qCT) parameters can quantify lung involvement in SSc and differentiate it from IPF [33].

Radiological deterioration mirrors functional deterioration and hence, it has been suggested to perform biannual CT scans to document disease progression [34]. The use of ultra-low-dose and AI-based quantitative CTs may make this possible in the recent future without any increased radiation risks to patients.

Ultrasound Screening for CTD-ILD

In the last decade, ultrasound has come up as a screening tool for ILD in CTD [35, 36]. It can also be used for prognostication. In SSc, the presence of more than 5 B-lines is associated with worsening ILD [37]. Despite its limitations, it detects sub-pleural disease that has a higher risk of progression. Moreover, it is inexpensive, less time-consuming, and widely available in rheumatology clinics where musculoskeletal ultrasound is practiced. Coupled with pulmonary function tests, it can be a valuable screening tool to screen for the need for a CT. Another upcoming modality is high-strength MRI that is non-ionizing and has also been shown to detect CTD-ILD [38].

Role of Serum Biomarkers for Screening and Monitoring

Out of various serum biomarkers proposed in the context of CTD-ILD, the strongest evidence is for SP-D (surfactant protein), KL-6 (Krebs von den Lungen-6), and CCL19 in SSc-ILD [39••]. KL-6 is a well-known biomarker for ILD in general. CCL19 can predict SSc-ILD progression [39••]. Even the tumour markers CA (carbohydrate antigen)-125 and CA19-9 have been studied as markers of epithelial damage and can predict short-term mortality [40]. Similarly, in RA-ILD, CA125, CA19-9, CEA (carcinoembryonic antigen), and KL-6 have been validated as biomarkers [41]. Other biomarkers for RA-ILD can include genetic polymorphisms of the MUC5B gene and serum interleukin-13 levels [20, 42]. Due to comparatively low sensitivity and specificity, serum biomarkers have not broken the cost–benefit barrier for commercial use.

Role of Lung Biopsy for Diagnosis

Since HRCT of the thorax provides fairly detailed information of lung structure and pathology [43], a lung biopsy is rarely required in the diagnosis or management of CTD-ILD.

When ILD develops in the setting of an established CTD and the diagnosis is straight forward, lung biopsy is not warranted. It may be useful in instances like suspected sarcoidosis where transbronchial biopsy may be utilized. Biopsy may be required to rule out more airway-centric complications such as bronchiolitis, hypersensitivity pneumonitis, sarcoidosis, or malignancy [44]. Lung tissue can be obtained via transbronchial biopsy (TBLB), transbronchial cryobiopsy (cryo-TBB), bronchoscopic ultrasound-guided biopsy, or video-assisted thoracoscopic surgery (VATS). Thus, open surgical lung biopsy via thoracotomy is rarely recommended in the setting of an ILD [45].

Treatment of CTD-ILD

There are limited trials on CTD-ILD as a whole. Most of the evidence is derived from the trial conducted in SSc-ILD patients. Also, there is some emerging data on the treatment of RA-ILD and myositis-associated ILD. However, the most challenging part is often to determine the risk–benefit ratio of different therapies for individual patients.

Identification of Patients Who Require Treatment

The OMERACT (outcome measures in rheumatic diseases) defines clinically meaningful progression of CTD-ILD as ≥ 10% relative decline in forced vital capacity (FVC) or ≥ 5% to < 10% relative decline in FVC and ≥ 15% relative decline in DLCO [46••]. Often, especially if the patient has no or minimal symptoms, it is appropriate to document clinically relevant progression of CTD-ILD before initiating treatment. Other than such decline in the PFT or the presence of symptomatic disease, a decision to treat could be made if the visually estimated volume of interstitial abnormalities is more than 20% of the total lung volume on imaging (CT) or the absolute FVC is less than 70%. The PaO2/FiO2 ratio is one of the strongest individual parameters to predict survival in CTD-ILD [47].

In RA-ILD, the presence of usual interstitial pneumonia (UIP) pattern with subpleural reticulation, traction bronchiectasis, and honeycombing usually is a harbinger of progressive disease [48]. Of these, the presence of honeycombing, regardless of the underlying pattern, has the strongest association with poor prognosis [49].

In SSc, the most active part of the disease is the first 4–5 years and the bulk of clinical trials include patients in these initial years only [7••]. Similarly, in most other CTDs, there is a perception that the longer the ILD has been present, the less likely it is to progress. Thus, there is limited logic or even evidence to treat CTD-ILDs beyond the initial 7–8 years of onset or detection.

The European consensus statements on CTD-ILD provide a framework of reference for monitoring patients and making a decision on treatment initiation or escalation [50•]. The essence of these guidelines is summarized in Table 2.

Role of Corticosteroids

Corticosteroid use will depend on the underlying CTD and extra-pulmonary manifestations. In most cases of SSc, corticosteroids are avoided as the possible harms outweigh the benefit [51]. In cases of MCTD-ILD and RA-ILD, there is adequate justification from the underlying disease to use appropriate (low to moderate) doses of steroids. Prednisolone 0.5 mg/kg body weight/day is used as the usual starting

Table 2 Summary of key recommendations of the European consensus statements on CTD-ILD [50•]

Area	Key recommendations
Risk factors	Ethnicity, gender, and the presence of autoantibodies such as anti-centromere, anti-topoisomerase, and anti-centromere antibodies influence the likelihood of a systemic sclerosis patient having or developing ILD Other biomarkers are not commonly used in clinical practice
Screening and diagnosis	All patients should have a baseline PFT The diagnostic tool is HRCT HRCT is recommended when symptoms (cough or dyspnoea) are present Severity should be assessed by a combination of PFT (FVC, DL_{co}, and their derivates), HRCT fibrosis score, and exercise-induced changes in blood oxygen saturation (6-min walk test) Early/stable/mild disease should be monitored every 3–6 months
Treatment initiation	Decisions for treatment should be based on the current disease state and the rate of progression Drivers for treatment choice include survival rate, response after treatment, prolongation of time to progression, speed of improvement of symptoms, safety and tolerability, and quality of life Mycophenolate and cyclophosphamide are effective for SSc-ILD
Treatment escalation	Speed of progression and disease severity should drive decisions for escalation Hemopoietic stem-cell transplantation and lung transplants are effective in specific subsets of SSc-ILD

ILD interstitial lung disease, *PFT* pulmonary function tests, *HRCT* high-resolution computerized tomography, *FVC* functional vital capacity, DL_{co} diffusion capacity of carbon monoxide, *SSc* systemic sclerosis

dose with a gradual taper over weeks to months depending on clinical response. Steroids are the standard of care for inflammatory myositis-associated ILD. Higher doses (1 mg/kg body weight/day of prednisolone) may be required at time of treatment initiation. In cases of IPAF, steroids may be considered depending on the autoimmune features present and the morphology of the ILD. Lymphocytic interstitial pneumonia and non-specific interstitial pneumonia (NSIP) have better response to corticosteroids than usual interstitial pneumonia (UIP) [45]. The dose and duration need to be individualized. Caution is warranted as the use of corticosteroids in IPF is associated with increased mortality [52].

Evidence from Systemic Sclerosis trials

The standard of care for SSc-ILD is mycophenolate (MMF) or cyclophosphamide (CYC) based on the seminal scleroderma lung studies I and II [53••, 54••]. Systematic reviews comparing MMF versus CYC have shown equal efficacy for both with possibly lesser adverse effects with MMF [55]. The role of anti-fibrotic to aid immunosuppressants in SSc-ILD is also promising [56••]. The major trials of SSc-ILD except for stem-cell transplantation (dealt with later) are summarized in Table 3.

The most important evidence come from the SLS (scleroderma lung studies) I and II [53••, 54••]. SLS I established the role of oral CYC for SSc-ILD. Oral CYC is often more toxic than monthly intravenous pulse CYC. Thus, the authors are more comfortable using pulse CYC for SSc-ILD. The SLS II showed the non-inferiority of MMF to CYC in the management of SSc-ILD. The number of death in the CYC arm was numerically more in SLS II. Though the difference was not statistically significant, the study was not powered to look at this. Thus, some authors make a case of first use of MMF in SSc-ILD and then to shift to CYC in case of MMF failure.

The SENSCIS trial [57••] is noteworthy for showing the benefit of nintedanib for CTD-ILD. However, if the fine print is read, unlike other trials where the relative decline of FVC was measured, in the SENSCIS trial, only absolute change in FVC was statistically different between the drug and placebo groups. Thus, until more data emerges, it may be prudent to take it with a pinch of salt.

Interestingly, the two common drugs used in the clinic for SSc-ILD, CYC, and MMF have not received approval of the US Food and Drug Administration (FDA) while nintedanib and tocilizumab have been approved [63].

Rituximab (RTX) is another drug that is used for SSc-ILD if refractory to CYC and MMF. It has not been explored in the context of a formal RCT. There is extensive real-world data on its use documented in the EUSTAR registry [64] and this has been validated with systematic reviews [65]. However, a recent prospective observation nested in the EUSTAR cohort showed only improvements in the skin but not in lung function with RTX [39••]. Thus, until more clear evidence is available, it may be appropriate to use RTX only after the failure of both MMF and CYC.

Evidence for Immunosuppression from Other CTD-ILDs

Table 4 summarizes the immunosuppressants that are the standard of care for different CTD-ILDs. The choice of a particular agent is governed by several factors (Fig. 1). The duration of therapy is debatable since evidence of long-term use is not available. Most trials have been for 6–24 months, and that is the basis of the recommendation of therapies in the short term [54••, 63]. In the experience of the authors, azathioprine may be a good option for long-term maintenance in both SSc-ILD and RA-ILD. This is especially true after cyclophosphamide therapy, the use of which is recommended for 6 months.

Evidence for CTD-ILDs other than SSc-ILD is limited to non-RCT studies only. The most important change in practice is the use of methotrexate (MTX) in RA-ILD. The evidence is quite clear that MTX protects from RA-ILD progression and does not exacerbate it as once thought [66, 67]. There is some evidence that anti-TNF (tumournecrosis factor) therapies may improve small airway disease in RA-ILD [68].

Myositis-ILD is in itself a heterogeneous entity with a myriad of clinical phenotypes and autoantibodies present. First-line drugs are often methotrexate and azathioprine but calcineurin inhibitors (cyclosporine and tacrolimus) and rituximab are gradually becoming more popular [69]. Some rapidly progressing phenotypes may require aggressive therapies. The rapidly progressing MDA-5 antibody phenotype has been treated with high-dose steroids with at least two of cyclophosphamide, tofacitinib, and rituximab [70••]. The JAK inhibitor tofacitinib may be useful in refractory cases [71] while other salvage therapies are rituximab and plasma exchange [72].

Role of Stem Cell Transplantation

For rapidly progressing patients with SSc-ILD without pulmonary hypertension, autologous haematopoietic stem cell transplant (AHSCT) has a definite role in the management. Despite many patients not meeting these criteria, it is a major step forward in therapeutics. Within the last decade, two trials [73, 74] have set the tone for exploring this avenue further (Table 5). These two trials and the preceding phase-two trial have shown that careful patient selection is required for optimal outcomes. The SCOT (Scleroderma: Cyclophosphamide or Transplantation) study was ended before the scheduled time because the interim analysis showed a clear benefit in the transplant arm [74••].

Table 3 Major trials of immunosuppressant and/or anti-fibrotic agents in systemic sclerosis–interstitial lung diseases

Trial name	No	Design	Arms	Outcome
FAST: Fibrosing Alveolitis in Scler oderma Trial [58]	$n = 45$	12-month randomized, double-blind, placebo-controlled trial	Prednisone 20 mg on alternate days + monthly CYC 600 mg/m^2 (6 months), then AZA 2.5 mg/kg/day; versus placebo	Adjusted relative treatment effect for FVC was 4.19% in favour of Rx ($P = 0.08$)
SLS 1: Scler oderma Lung Study-CYC [53••]	$n = 158$	1-year, randomized, double-blind, placebo-controlled trial plus 1 additional year of follow-up without study medication	Oral CYC ≤ 2 mg/kg; versus placebo	Mean absolute difference in adjusted 12-month FVC: 2.53% (95% CI 0.28, 4.79), favouring CYC ($P < 0.03$): up to 24 months
SLS 2: Scler oderma Lung Study-MMF [54••]	$n = 142$	2-year, randomized, double-blind, superiority trial	MMF (1500 mg twice daily) for 24 months versus oral CYC (2·0 mg/kg/day) for 12 months followed by placebo for next 12 months	Primary end-point of the superiority of MMF not met. But both groups had significant improvement in pre-specified measures (lung function, dyspnoea, lung imaging, and skin disease). CYC group had numerically more adverse effects
LOTUSS: Pir fenidone safety [59••]	$n = 63$	16-week randomized, open-label comparison of two titration schedules	Pirfenidone 801 mg TDS (2-week titration); pirfenidone 801 mg TDS (4-week titration)	More patients discontinued treatment because of TEAEs in the 2-week arm ($n = 5$) than in the 4-week arm ($n = 1$)
SENSCIS: Nintedanib [57••]	$n = 576$	54-month randomized, double-blind, placebo-controlled trial	150 mg of nintedanib orally twice daily; versus placebo	Annual rate of change in FVC was − 52.4 ml in the nintedanib group and − 93.3 ml in the placebo group (difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; $P = 0.04$)
FaSScinate: Tocilizumab [27••]	$n = 87$	48 weeks randomized, double-blind, placebo-controlled trial	Subcutaneous TCZ 162 mg; versus placebo	The primary end point was not met. However, differences in FVC: Placebo:, − 3.9 [− 7.2, 0.6] vs TCZ, − 0.6 [− 5.3, 3.9]; $p = 0.0015$
FocuSSed trial Tocilizumab [60]	$n = 210$	48 weeks randomized, double-blind, placebo-controlled trial	subcutaneous tocilizumab 162 mg or placebo	Primary skin fibrosis endpoint was not met. change from baseline in FVC% predicted at week 48 favoured tocilizumab ($p = 0{\cdot}002$)
Naidu et al. [61]	$n = 41$	Double-blind, randomized, placebo-controlled trial	either MMF (2 g/day) or placebo for 6 months	FVC decreased by a median of 2.7% (range — 21 to 9) in MMF arm and increased by 1% (range — 6 to 10) in placebo arm ($p = 0.131$)
Acharya et al. [62]	$n = 35$	Double-blind, randomized, placebo-controlled	Pirfenidone (2400 mg/day) or placebo for 6 months	Stabilization/improvement in FVC was seen in 16 (94.1%) and 13 (76.5%) subjects in the pirfenidone and placebo groups, respectively ($p = 0.33$)

CYC cyclophosphamide, *MMF* mycophenolate mofetil, *TCZ* tocilizumab, *AZA* azathioprine, *FVC* functional vital capacity, *TEAE* treatment emergent adverse events

Table 4 Standard immunosuppressants used in different CTD-ILD

CTD	Drugs	Remarks
SSc-ILD	Mycophenolate 2–3 g daily orally Cyclophosphamide Oral: 2–3 mg/kg body weight/day Pulse: 600/m^2 iv every month For a maximum of 6 months Nintedanib may be added to either of the above at 150 mg 12 hourly orally	Pulse CYC doses are associated with lesser toxicity but most trials have used daily oral doses Rituximab (2 g induction as given below) and tocilizumab (162 mg subcutaneous weekly) are second-line agents
RA-ILD	Rituximab 1 g intravenous infusion 2 weeks apart Azathioprine 2–3 mg/kg body weight/day orally Cyclophosphamide (as mentioned above) Mycophenolate 2–3 g daily orally	Methotrexate and leflunomide may have a role especially in early minimally symptomatic disease A proportion of RA-ILD do not progress or progress very slowly even without treatment
Myositis-ILD	High doses steroid (1 mg/kg body weight of prednisolone) with one of the following: Rituximab 1 g 2 weeks apart (Or 375 mg/m^2 body surface area weekly × 4 weeks) Mycophenolate 2–3 g daily orally Azathioprine 2–3 mg/kg body weight/day Cyclophosphamide (as mentioned above)	Rapidly progressing disease: Pulse steroids with one or two of the following: Rituximab, cyclophosphamide, tofacitinib, or intravenous immunoglobulin

Dosages may need adjustment for hepatic or renal dysfunction

CTD connective tissue disorders, *RA* rheumatoid arthritis, *ILD* interstitial lung disease

Beyond the controlled trials, there is also evidence for AHSCT from transplant registries [76, 77]. In the registry data, mortality was around 6% mostly attributable to cardiac and cyclophosphamide toxicity [77].

Non-pharmacological Therapies

A multi-disciplinary effort is required in CTD-ILD [78]. There are a host of non-pharmacological therapies

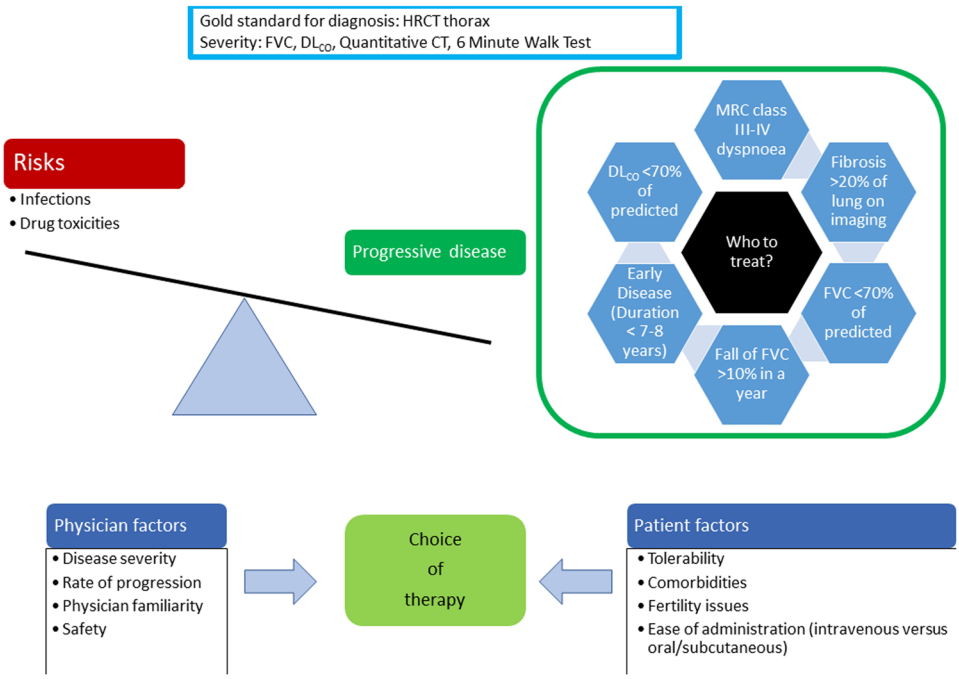

Fig. 1 Deciding on who and how to treat

Table 5 Trials involving stem cell transplantation for systemic sclerosis–associated interstitial lung diseases

Trial	Participants	Design	Arms	Outcome
ASSIS T (American scleroderma stem cell versus immune suppression trial, phase II) [75]	$N = 19$	Open-label, randomized, controlled phase 2 trial	1. HSCT, 200 mg/kg intravenous cyclophosphamide, and 6·5 mg/kg intravenous rabbit anti-thymocyte globulin 2. Versus to receive 1·0 g/m(2) intravenous cyclophosphamide once per month for 6 months	8/9 controls had disease progression compared with no patients treated by HSCT ($p = 0.0001$)
ASTIS: Autologous Stem Cell Transplantation International Scleroderma [73]	$n = 156$	Randomized, open-label, active comparator survival study	1. CYC 750 mg/m^2/month; post-myeloablation CD34$^+$-selected autologous HSCT 2. 12 monthly pulses of intravenous cyclophosphamide (750 mg/m^2)	During follow-up (median 5.8 years), 53 events occurred (HSCT, $n = 22$; CYC, $n = 31$)
SCOT Scleroderma: Cyclophosphamide or Transplantation [74••]		54-month randomized, open-label, active comparator study	1. CYC 750 mg/m^2/month; post-myeloablation CD34$^+$-selected autologous HSCT 2. 12 monthly pulses of high-dose intravenous cyclophosphamide (an initial dose of 500 mg/m^2, followed by 11 doses of 750 mg/m^2)	Event-free survival was 50% with CYC and 79% with HSCT ($P = 0.021$) Composite GRCS score comparisons favoured HSCT (48 months, $P = 0.008$; 54 months, $P = 0.013$)

HSCT hemopoietic stem cell transplant, *CYC* cyclophosphamide, *GCRS* global composite rank score

to supplement management, specially in patients with advanced disease.

Vaccination

All patients with CTD-ILD should be vaccinated with adult vaccines recommended for persons having chronic lung diseases [79]. The basic vaccines include influenza and pneumococcal vaccines [80]. Often vaccination in persons with lung diseases is less than ideal [81]. Both patient-focussed and clinician-focussed activities are required to increase vaccination coverage in susceptible people with CTD-ILD [82].

Pulmonary Rehabilitation

Pulmonary rehabilitation includes exercise training, education, and behaviour change [83]. Patients must be advised to stop smoking. Physical activity and exercise training can improve both functional status and quality of life [84]. Pulmonary rehabilitation has been shown to benefit in stable ILD regardless of disease severity [85].

Management of Comorbidities

It is often the comorbidities that lead to added susceptibility to infections including COVID-19 [17]. Sometimes the dyspnoea attributed to the ILD may be actually due to pulmonary hypertension or associated myositis or cardiac disease due to the underlying CTD. Thus, these must be adequately addressed. Sarcopenia is common in symptomatic ILD and should be corrected with proper diet and physical activity [86].

Palliative Care and Oxygen Therapy

At end-stage fibrosis with dyspnoea at rest, there is an unmet need for adequate palliative care [87]. This includes effective pharmacological and psychosocial interventions to ease daily functioning. Palliative care should not be restricted only to end-of-life situations. Social isolation and lack of communicationdue to persistent dyspnoea can be challenging problems [88].

Oxygen therapy has shown to improve exercise capacity but has limited effects on dyspnoea [89••]. Long-term oxygen therapy is a standard of care for resting hypoxemia and ambulatory oxygen may help exertional hypoxemia [90]. There exist guidelines for effective home oxygen therapy that may be utilized for CTD-ILD [91].

Lung Transplantation

Lung transplantation may be considered for end-stage CTD-ILD. In the presence of severe pulmonary

Table 6 Registered clinical trials for CTD-ILDs

Trial number	Title	Drug	Disease	Trial estimated end-date
NCT04948554	Study of ACE-1334 to Evaluate the Safety, Pharmacokinetics, Pharmacodynamic Effects, and Efficacy in Participants With Systemic Sclerosis With and Without Interstitial Lung Disease	Recombinant homodimeric Fc fusion protein comprising of the extracellular domain (ECD) of the human TGF-βRII, linked to a modified human Fc domain of IgG1	SSc-ILD	December 2027
NCT03221257	Scleroderma Lung Study III — Combining Pirfenidone With Mycophenolate	Pirfenidone with mycophenolate	SSc-ILD	June 2022
NCT04837131	A Study to Evaluate the Safety and Tolerability of Oral Ixazomib in Scleroderma-related Lung Disease Patients	Proteasome inhibitor ixazomib	SSc-ILD	April 2024
NCT03919799	A Phase 2, Randomized, Placebo-controlled, Double-blind, Open-label Extension Multicenter Study to Evaluate the Efficacy and Safety of Belumosudil (KD025) in Subjects With Diffuse Cutaneous Systemic Sclerosis	Belumosudil: inhibitor of Rho-associated coiled-coil kinase 2 (ROCK2)	SSc-ILD	December 2021
NCT03084419	Safety of Abatacept in Rheumatoid Arthritis Associated Interstitial Lung Disease: A Feasibility Trial	Abatacept	RA-ILD	March 2020 (outcomes not reported yet)
NCT04311567	Effects of Tofacitinib vs Methotrexate on Rheumatoid Arthritis Interstitial Lung Disease (PULMORA)	Tofacitinib/methotrexate	RA-ILD	May 2024
NCT02808871	Phase II Study of Pirfenidone in Patients With RAILD (TRAIL1)	Pirfenidone	RA-ILD	April 2021 (outcomes not reported yet)
NCT02821689	Pirfenidone in Progressive Interstitial Lung Disease Associated With Clinically Amyopathic Dermatomyositis	Pirfenidone	Clinically amyopathic dermatomyositis-ILD	June 2018 (outcomes not reported yet)
NCT03813160	Trial to Evaluate Efficacy and Safety of Lenabasum in Dermatomyositis (DETERMINE)	Lenabasum (type 2 cannabinoid receptor agonist)	Dermatomyositis	March 2021 (outcomes not reported yet)

hypertension, a combined heart–lung transplant may be required. Since organs for transplant are a very precious resource, there are strict recommendations on choosing the correct patient for such transplants [92••]. Patients with non-myositis CTD-ILD have cumulative survival levels equal to those with IPF. However, patients with myositis-ILD often have a worse post-operative period and poorer outcomes [93]. In the case of SSc-ILD also, the rate of graft survival mirrors those of IPF.

Exploratory Therapies

Various therapies have been tried in the context of phase 1/2 trials for SSc including inebilizumab (anti-CD19), dabigatran, Wnt signaling blocker C-82, pomalidomide (anti-angiogenic and immunomodulator of lymphocytes and myelocytes), rilonacept (IL-1 receptor analog), romilkimab (bispecific antibody against IL-4 and IL-13), lenabasum (type 2 cannabinoid receptor agonist), abatacept (co-stimulation blocker), belimumab (anti-BAFF, B cell–activating factor), riociguat (soluble guanylate cyclase stimulator), and lanifibranor (PPAR agonist) [94]. A phase II study of abituzumab in SSc-ILD was terminated due to very low recruitment [95]. The various RCTs registered in clinical trials for CTD-ILDs are summarized in Table 6.

Future Avenues

The main challenge facing the treating clinician is disease heterogeneity as different diseases underlie CTD-ILD. Even for the same sub-group with a similar autoantibody profile, the clinical progression and response to treatment vary. Immunosuppression needs to be balanced with the risk of infections that are not uncommon in these patients and may even be fatal.

The future lies in personalized precision medicine [96]. Beyond the recognition of clinical phenotypes, a combined multi-omics (genetic, methylomics, transcriptomics, and proteomics) approach is expected to classify patients into rapid progressors, slow progressors, or very slow progressors. This will help guide the timing of therapy and hopefully predict response to different drug groups enabling the clinician to choose the optimum combination of immunosuppressants, anti-fibrotics, and immune re-booting procedures such as autologous haematopoietic stem cell transplantation.

Limitations of the Review

We have not considered sarcoidosis and vasculitis-associated ILD under the umbrella of CTD-ILD. There are case series and observational data for many more therapies in different

CTD-ILDs. However, we have focussed only on therapies with robust evidence by way of controlled trials or registry data.

Conclusion

The heterogeneity of CTD-ILDs and the limited, but expanding, evidence make the task of the clinician exciting yet challenging at the same time. The advent of novel therapeutic agents with the application of biomarkers to stratify patients is a work in progress.

Compliance with Ethical Standards

This is a review of published literature and does not require ethics clearance.

Conflict of Interest SA has received honorarium as speaker from Pfizer, Dr Reddy's, Cipla and Novartis (unrelated to the current work). RH has served as speaker, consultant, advisory board member for Abbott India, Pfizer, IPCA, Janssen, Eli Lilly, Novartis (unrelated to the current work). No conflict of interest pertaining to this work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer All views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any institution or association.

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