Treating connective tissue disease-associated interstitial lung disease – think outside the box: a perspective

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A pharmacotherapeutic approach based on the concept of preventative medicine offers a framework for research development and clinical practice of goal-focused treatments at different disease stages of connective tissue disease-associated ILD. https://bit.ly/4ksDHjj

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Abstract

Connective tissue disease-associated interstitial lung disease is one of the most common subtypes of interstitial lung disease, which is a leading cause of morbidity and mortality in patients with these systemic autoimmune rheumatic diseases. A spectrum of disease trajectories exists within individual and across different connective tissue diseases. In individuals with connective tissue diseases who are at risk or at the early asymptomatic stage with interstitial lung changes, we have potential windows of opportunity for interventions to prevent the development of or progression to interstitial lung disease. In this perspective, we use systemic sclerosis and rheumatoid arthritis as sample cases to discuss emerging knowledge on disease pathogenesis, as well as to apply the preventative medicine concept for pharmacotherapeutic approaches at different disease stages of connective tissue disease-associated interstitial lung disease.

Introduction

Connective tissue diseases (CTDs) of autoimmune origin refer to a heterogeneous group of multisystem chronic conditions characterised by dysregulation of the immune system with the production of autoantibodies. The burden of CTDs has risen over the years, with recently reported incidence rates ranging between 3.3 and 149.2 per 100 000 person-years for individual diseases in a recent population study [1]. Interstitial lung disease (ILD) is a key disease manifestation of leading morbidity and mortality in patients with most CTDs [2–6], despite variation in its prevalence and presentation across different CTDs [7]. CTD-associated ILD (CTD-ILD), recently also introduced as systemic autoimmune rheumatic disease-related ILD [8, 9], is one of the most common forms of ILD encountered clinically. It poses a substantial economic burden, with estimated annual healthcare costs of over EUR 13 700 per person for pharmacological and non-pharmacological interventions [10]. Furthermore, CTD-ILD often affects individuals of working age, leading to decreased workplace productivity, with an estimated loss of CAD 13 593 per employee annually in 2017, the latest available evidence [11]. In light of this, we have used systemic sclerosis (SSc) and rheumatoid arthritis (RA) as illustrations to provide a focused overview of key aspects of the pathogenesis of CTD-ILDs and to propose pharmacotherapeutic approaches for each disease stage through the public health concept of preventative strategies [12].

A spectrum of trajectories exists within individual and across different CTDs, which ranges from non-progressive and slow-evolving disease to rapid deterioration with varying responses to immunosuppressive drugs, even in the same autoimmune diseases (figure 1). Up to 45% of patients with CTD-ILD develop progressive pulmonary fibrosis, with health outcomes and survival similar to those of patients with idiopathic pulmonary fibrosis (IPF) [13, 14]. Despite this heterogeneity in disease presentations and courses of CTD-ILD, distinct disease stages could be classified by adapting the Global Initiative for Chronic Obstructive Lung Disease classification for COPD [15]: a susceptible stage for individuals with a known CTD but no evidence of lung involvement (CTD-ILD-0), a very early disease stage for individuals with a known CTD and clinically asymptomatic lung involvement (CTD-ILD-A), and the clinical symptomatic stage for individuals with established CTD-ILD (CTD-ILD-B). CTD-ILD-B can be further subdivided into inflammation-predominant, fibrosis-predominant and mixed inflammatory/fibrotic phenotypes, with various disease trajectories ranging from stable, slowly or rapidly progressive, or with episodes of acute exacerbation (CTD-ILD-E) (figure 2). Other manifestations in CTDs may affect the disease course of ILD [16], such as gastro-oesophageal reflux disease and pulmonary hypertension, with the latter being common in those with SSc who have anti-centromere antibodies [17], which can be labelled with a plus sign following the CTD-ILD stages (*e.g.* CTD-ILD-B+). This conceptual framework presents different therapeutic opportunities to prevent or minimise progression and reduce undesirable health outcomes in patients with CTD-ILD. We chose SSc and RA to represent the spectrum of inflammation-predominant and fibrosis-predominant CTD-ILDs in this perspective.

Pathogenesis for ILD in CTDs

While different cellular and molecular pathways are involved in the disease mechanisms of SSc and RA, both inflammatory and fibrotic processes are closely intertwined and can overlap and occur in parallel.

Inflammatory processes in CTDs and autoantibodies

Key characteristic histopathological features of CTD-ILD include extensive plasma cell infiltration, increased lymphoid aggregates and more germinal centres, suggesting the importance of inflammation [18, 19]. Autoantibody production with loss of self-tolerance is a hallmark of different CTDs and is postulated to play a key role in the inflammatory process.

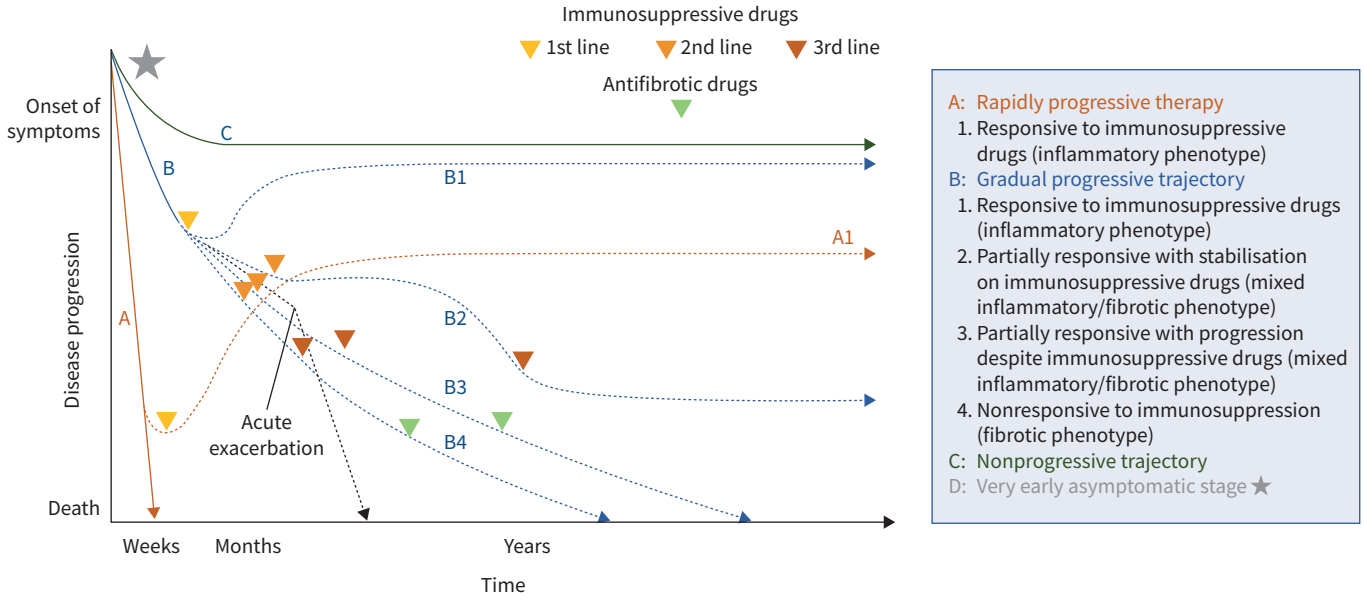

FIGURE 1 Clinical trajectories of connective tissue disease-associated interstitial lung disease (CTD-ILD). Patients with CTD-ILD have several possible disease courses. Patients may have rapidly progressive disease that is typically responsive to a single or multiple immunosuppressive drugs (line A), while others may have nonprogressive disease (line C). A substantial number of patients experience gradual progressive disease (line B), which has varying treatment responses to immunosuppressive drugs and may need additional antifibrotic drugs. Solid lines represent an untreated state. Of note, acute exacerbation may occur in patients with CTD-ILD, leading to sudden deterioration. Some patients with CTD may have very early asymptomatic stage disease (grey star) with incidental findings on screening, which has been termed as subclinical ILD and pre-pulmonary fibrosis.

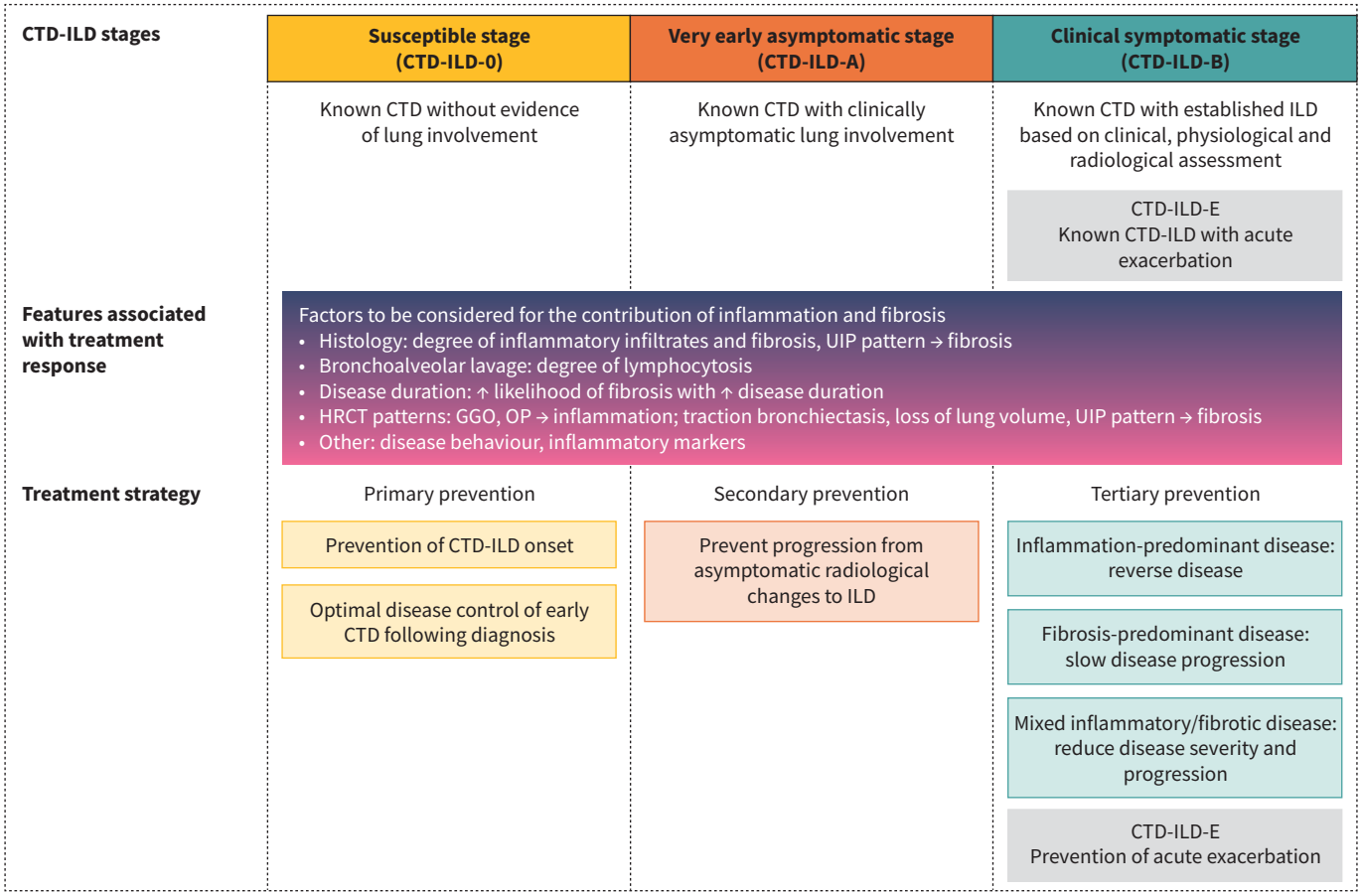

FIGURE 2 Proposed disease stages and treatment strategies for connective tissue disease-associated interstitial lung disease (CTD-ILD). A plus sign may be added following the CTD-ILD stages (*e.g.* CTD-ILD-B+) to indicate the presence of other manifestations in CTDs that may affect the disease course of ILD, such as gastro-oesophageal reflux disease and pulmonary hypertension. GGO: ground-glass opacification; HRCT: high-resolution computed tomography; OP: organising pneumonia; UIP: usual interstitial pneumonia.

The autoantibodies develop early, even years before the onset of clinically apparent disease, and may have a direct pathogenic role [20, 21]. In patients with SSc, anti-topoisomerase I antibodies are detected and found to correlate with the manifestation of ILD [22–25]. Other identified autoantibodies with potential pathogenic roles in SSc include anti-endothelial cell, antifibrillin-1, anti-matrix metalloproteinase, antiplatelet-derived growth factor receptor, anti-angiotensin-1 receptor and anti-endothelin-1 type A receptor antibodies [26]. There is also a known association between SSc-ILD and anti-Ro52 antibodies, as seen in other CTD-ILDs, which may confer increased risks of ILD severity [27]. In patients with RA, there is accumulating evidence suggesting that the lungs are a priming site to generate anti-cyclic citrullinated protein (anti-CCP) antibody, the hallmark autoantibody [28]. While there is a lack of studies that have evaluated the pathogenic role of autoantibodies in the development of ILD in patients with RA, the anti-CCP antibody has been shown to activate macrophages and induce tumour necrosis factor-α [29]. The presence of anti-CCP antibody and rheumatoid factor is also associated with increased systemic inflammation and disease activity in patients with RA [28].

The association of specific autoantibodies in CTDs with clinical phenotypes also suggests that they have a role in disease pathophysiology. Of the different antibodies in patients with SSc, the presence of anti-topoisomerase 1 antibodies is associated with the manifestation of ILD [23]. Patients with RA and anti-CCP antibody have increased risk of RA-associated ILD (RA-ILD) [30], with fine-specificity anti-CCP antibodies recently identified as linking with incident cases [31]. Autoantibodies may be associated with specific radiological patterns of ILD. A recent study of patients with SSc-ILD reported that anti-CCP antibody positivity was associated with increased incidence of usual interstitial pneumonia (UIP) pattern and reduced ground-glass opacities on high-resolution computed tomography (HRCT) [32], although an overlap between SSc and RA cannot be excluded. Nevertheless, there are still unsolved

controversies, because these autoantibodies can be present in patients with CTD who have no lung manifestations as well as in healthy individuals [33–36]. There may be interplay among other factors, such as genetic risk and environmental exposures, causing individual mosaics of disease pathways and manifestations in patients with CTD. Notably, many genetic risk profiles identified for SSc and RA implicate immune pathways, such as protein tyrosine phosphatase non-receptor type 22 polymorphism related to T-cell receptor signalling in RA [37, 38].

Taken together, these findings suggest at least partial contributory roles for inflammation as a result of immune dysregulation, with autoantibody production among other predisposing risk factors in the development of ILD among patients with CTD.

Fibrotic processes of CTDs

Fibroblasts are central to the pathogenesis of lung fibrosis, including CTD-ILD. Circulating and alveolar fibrocytes, which are precursor cells of lung fibroblasts and myofibroblasts, are elevated in patients with SSc-ILD and RA-ILD, as seen in patients with IPF [39–41]. Chemokine expression of an M2 profibrotic phenotype profile for activated macrophages and T-cell profiles with increased CD4 to CD8 T-cell ratio and T-helper 17 (Th-17) levels are observed in patients with SSc-ILD [42]. Of the B- and T-cell cytokine profiles in SSc-ILD, interleukin (IL)-6 is consistently found to stimulate fibroblasts [43]. In RA-ILD, Th-17-cell-mediated immunity may be implicated in the development of lung fibrosis. Upregulated IL-17A receptor expression has been shown in areas of fibroblast foci and fibrosis of lung tissues from patients with RA-ILD, with IL-17A inducing fibroblast proliferation and promoting myofibroblast differentiation [44, 45]. Persistent activation of fibroblasts results in dysregulated metalloproteinase secretion, with increased collagen and extracellular matrix deposition [46]. As seen in IPF, alveolar epithelial cell injury, and the loss of progenitor cells through senescence and an accumulation of transitional cells as identified in recent transcriptomic studies, are also implicated in impaired lung reports and a profibrotic lung environment in CTD, which has primarily been evaluated in patients with SSc-ILD [47–49]. Epithelial biomarkers, such as serum levels of Krebs von den Lungen-6 and surfactant protein-D, are associated with lung disease severity and are of prognostic significance in patients with CTD-ILD, including SSc and RA [50–52].

Some genetic variants and mutations that have been implicated in IPF and familial pulmonary fibrosis are associated with RA-ILD but have not been observed in SSc-ILD or other CTD-ILDs [53]. These include telomere-related gene mutations and mucin-5B (*MUC5B*) promoter polymorphism (rs35705950). Telomeres are specific protein structures consisting of highly conserved tandem nucleotide repeats that are located at distal regions of chromosomes and prevent chromosomal degradation. Telomere dysfunction causes lung fibrosis in animal models [54–56]. In a French observational study, patients with RA-ILD had shorter telomere lengths and a higher burden of telomere-related gene mutations, including telomerase reverse transcriptase, regulator of telomere elongation helicase-1 and poly(A)-specific ribonuclease, compared to healthy controls with no known lung disease [57]. There is a similar observation of shorter peripheral blood leukocyte telomere length in patients with RA-ILD than in those with RA without ILD [58].

MUC5B encodes a mucin precursor protein involved in airway mucus production and homeostasis. Overexpression may result in mucociliary dysfunction and disruption of normal reparative mechanisms, contributing to lung fibrosis [59]. In patients with RA, the *MUC5B* promoter variant rs35705950 is associated with increased risk of ILD, particularly among those with a radiological UIP pattern [60, 61]. Furthermore, the *MUC5B* promoter variant rs35705950 may alter the clinical phenotype of patients with RA, with reduced time to onset of ILD [62]. However, the presence of this variant has not been found to affect transplant-free survival and lung function trajectories in patients with RA-ILD [63].

While the exact molecular mechanisms of inflammatory and fibrotic pathways for the development of ILD in patients with CTD are yet to be fully elucidated, accumulating knowledge over the recent years sheds light on potential therapeutic targets. Herein, we discuss potential application of the public health concept of preventative strategies in the management of CTD-ILD.

Susceptible stage (CTD-ILD-0): primary prevention pharmacotherapies

The development of ILD in approximately two thirds of patients with CTD, apart from those with idiopathic inflammatory myopathies, is preceded by a phase of autoimmunity and extrapulmonary manifestations. This may provide opportunities for early intervention in at-risk patients to prevent ILD onset or alter its disease course, which can be viewed as primary prevention of CTD-ILD to reduce both its incidence and disease burden. Current evidence suggests two possible approaches for primary prevention of CTD-ILD: 1) prevention of CTD onset and 2) optimal disease control of early phases of CTD following diagnosis, by targeting inflammatory pathways.

There are no currently approved pharmacotherapies for CTD prevention. In an observational study of patients with SSc with no sign of ILD on HRCT, early treatment with immunosuppressive drugs within 3 years of diagnosis did not significantly reduce the incidence of ILD [64]. However, this study was limited by the retrospective study design, with potential bias and confounders. Most studies have focused on preventing RA development, with no effects found with systematic corticosteroids, atorvastatin or hydroxychloroquine [65–67]. However, recent placebo-controlled randomised controlled trials (RCTs) of disease-modifying antirheumatic drugs (DMARDs) in at-risk individuals for RA provide promising results on delaying onset or reducing symptoms of extrapulmonary symptoms and signs, including the PRAIRI trial of a single-dose rituximab [68], the TREAT EARLIER proof-of-concept trial of 1-year methotrexate with a single-dose intramuscular glucocorticoid injection [69], the phase 2b APIPPRA trial of 1-year abatacept [70] and the ARIAA trial of 6-month abatacept [71]. The most appealing preventative intervention might however be smoking cessation, because smoking is an important risk factor for the development of seropositive RA and RA-ILD [72]. A recent analysis of the Nurses' Health Study I and II reported that smoking cessation delayed or even prevented the development of seropositive RA [73].

The majority of patients with CTD present with extrapulmonary manifestations, although some may have ILD as the first presentation [19, 74]. Given that increased disease activity levels and elevated systemic inflammatory markers are risk factors for ILD in patients with CTD [7], optimal disease control of early phases of CTD following diagnosis is a potential strategy to prevent the development of ILD. Following the initial concept of early SSc [75], the contemporary concept and criteria based on clinical signs and the presence of specific autoantibodies for the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) was introduced in 2011 [76]. The VEDOSS criteria have been validated, with established risk stratification based on the absence of antinuclear antibodies, positive SSc-specific autoantibodies and the presence of puffy fingers for increased risk of SSc progression [77]. In a recent preliminary trial of methylprednisolone in individuals with VEDOSS, no clinically relevant efficacy was observed, with 37% experiencing disease progression and 23% having lung function decline [78]. In patients with RA, the treat-to-target approach aiming for tight disease control and early remission is the standard of care; however, it is uncertain whether different DMARDs have varying effects on modulating the development of ILD in CTD. Methotrexate, a conventional synthetic DMARD, remains the first-line therapy for patients with RA [79, 80]. While methotrexate use in patients with RA-ILD has long been the subject of controversial debate, recent observational studies add to previous meta-analyses on its potential protective effects against RA-ILD [81–84]. In the latest international multicentre case–control study of 1083 patients with RA, patients with RA-ILD were less frequently treated with methotrexate compared to those without ILD, with ILD detection delayed by 3.6 years [82]. Tocilizumab, a biological DMARD inhibiting IL-6, was evaluated in the U-Act-Early RCT in 317 patients with RA diagnosed within 1 year [85]. Tocilizumab with or without methotrexate was more effective than methotrexate in achieving sustained disease remission, defined by the Disease Activity Score-28 and the number of swollen joints, with relative risks of 2.00 and 1.86, respectively. This approach to preventing ILD development thus warrants further evaluation.

Understanding preventative and early intervention approaches in CTD is particularly relevant in advancing the primary prevention of ILD in this population. These studies highlight the potential modulating effects of B-cell- and T-cell-directed therapies on disease mechanisms, particularly in RA. However, preventative clinical trials for RA have not focused on the development of ILD and they have had limited follow-up durations. The prevention of ILD may, therefore, be better assessed in longer-term observational studies. Furthermore, strategies for risk stratification to identify specific subgroups at high risk of ILD development or progressive lung disease are needed to avoid overtreatment and/or iatrogenic harm.

Very early asymptomatic stage (CTD-ILD-A): secondary prevention pharmacotherapies

Different terminologies have been used to describe the very early disease stage of CTD-ILD, including subclinical ILD and pre-pulmonary fibrosis. The recent guidelines by the American College of Rheumatology and American College of Chest Physicians provide the first recommendation for screening for ILD in at-risk patients with CTDs using lung function assessment and HRCT [8]. A risk-stratifying scoring system for ILD screening in asymptomatic patients with RA has recently been proposed, and includes male sex, age ⩾50 years, ever-smoking history, pack-years, disease duration >5 years, persistent moderate-high disease activity based on the Disease Activity Score-28, higher titres of rheumatoid factor and anti-CCP, and family history of ILD [86]. While *MUC5B* gene mutations are an important risk factor for the development of ILD in patients with RA, this has not been included in the scoring system owing to the limited access to genetic testing in clinical care. Of note, similar risk factors for the development of ILD, including demographics, measures of disease activities and autoantibody profiles, are observed in patients with SSc [7]. In an observational study of 305 patients with SSc who underwent screening CT and lung function tests, 51% had limited ILD defined as 1–20% of lung involvement on CT [87]. Subclinical

ILD, a very early asymptomatic stage, is reported to affect between 17% and 44% of patients with RA, and is associated with increased all-cause mortality [88–93]. As we learnt from studies of interstitial lung abnormalities in the general population and lung cancer screening or smoker cohorts, which are defined as nondependent radiological abnormalities involving ⩾5% of a lung zone, approximately 20% of individuals develop progressive changes over 2 years [94]. Effective secondary prevention to prevent progression to ILD in these populations can ameliorate the associated high morbidity and mortality burdens of ILD, and may be achieved with targeted immunosuppression or immunological reset.

Recent RCTs of tocilizumab in SSc demonstrated potential treatment effects on early ILD. These RCTs enrolled patients with early diffuse SSc of disease duration ⩽60 months and elevated inflammatory markers [95, 96]. In the phase 2 faSScinate trial of 87 patients, fewer patients receiving tocilizumab had a decline in forced vital capacity (FVC) % predicted at 48 weeks as an exploratory end-point, with the primary end-point of skin fibrosis score showing a trend for improvement over placebo [95]. The subsequent phase 3 focuSSced trial of 210 patients showed similar findings, with a reduced decline in FVC % predicted over 48 weeks, by −0.6% for tocilizumab compared to −4.0% for placebo (p=0.0002), although the primary end-point of change in skin score was not met [96]. Effects of FVC stabilisation with tocilizumab were consistent irrespective of the extent of lung parenchymal involvement on CT in *post hoc* analyses [97], and were maintained in the open-label phase until 96 weeks [98]. Given the mechanism of action of tocilizumab, serious infection was the primary adverse event. Nevertheless, tocilizumab was generally well tolerated, with discontinuation rates due to adverse events of <3% during the phase 3 trial and open-label phase. On the other hand, there have been no RCTs or high-quality observational studies evaluating interventions for preclinical and/or early ILD in patients with RA.

Other potential pharmacotherapies for secondary prevention of ILD in patients with CTD include rituximab and chimeric antigen receptor (CAR) T-cell therapy, with both targeting B-cell depletion. As mentioned earlier, B-cells are pivotal in the pathogenesis of the inflammatory phase of CTD, including SSc and RA, through their key functions of antibody production, cytokine production, antigen presentation and T-cell activation through costimulation molecules [99, 100]. Rituximab is a chimeric monoclonal antibody against CD20 surface antigen of immature and mature B-cells, except for plasma cells. Since its introduction in the 1980s, indications for rituximab have expanded from the management of lymphoproliferative disorders to autoimmune diseases, including CTDs [101]. In recent years, there has been mounting evidence for the efficacy of CAR T-cell therapy in CTD since the first case study in a patient with systemic lupus erythematosus in 2021 [102]. Similar to rituximab, CAR T-cell therapy was initially developed for treating haematological malignancies, with the engineered synthetic receptors promoting immunological reactions against cells expressing a specific target antigen by T-cells and other lymphocytes [103]. This approach has the potential of achieving B-cell reconstitution with drug-free remission following transient B-cell aplasia [104]. In cases of SSc with and without ILD, CD19-targeted CAR T-cell therapy led to improved disease manifestations [105–107]. *In vivo* assessment using mouse models of RA shows that CAR T-cell therapy targeting major histocompatibility complex molecules such as human leukocyte antigen complex DR alleles significantly suppressed CD4 T-cell response and autoantibody production, with reduced incidence and severity of arthritis [108]. Nevertheless, there are safety considerations with CAR T-cell therapy, particularly cytokine release syndrome as a result of its activation upon target cell engagement and neurotoxicity [104].

There is a pressing need for studies evaluating the more aggressive top-down approach of high-intensity immunosuppression in patients with CTD and very early ILD who are at risk of disease progression. This top-down approach may be superior for achieving and maintaining remission, as well as more cost-effective with the avoidance of long-term immunosuppression and morbidity, compared to the standard conservative approach with treatment initiation as ILD progresses. Despite the lack of biomarkers that are indisputably associated with disease progression in CTD-ILD to date, there are a few potential candidates, including radiological patterns and disease extent, inflammatory markers and autoimmune disease activities, in addition to selected autoantibodies and epithelial biomarkers mentioned previously [109–113].

Clinical symptomatic stage (CTD-ILD-B): tertiary prevention pharmacotherapies

In the clinical stage with an established diagnosis of CTD-ILD, tertiary prevention pharmacotherapies aim to treat according to the phenotypes to reverse disease severity in those with inflammation-predominant disease, to slow disease progression in those with fibrotic disease, and to reduce disease severity and progression in those with mixed inflammatory/fibrotic disease. Using data from published RCTs, stepwise approaches of immunosuppressive and antifibrotic drugs for SSc-ILD and RA-ILD are discussed. There may be crossover actions between immunosuppressive and antifibrotic drugs, because they often work on multiple pathways of different actions, with the drugs being classified based on the primary known effects. Of note, nerandomilast,

a preferential inhibitor of phosphodiesterase 4B with both anti-inflammatory and antifibrotic effects *in vitro* and *in vivo*, demonstrates the benefit of slowing FVC progression in progressive pulmonary fibrosis based on a preliminary report [114, 115]. To date, apart from histopathological samples, there is a lack of definitive noninvasive tests for distinguishing between inflammation and fibrosis in patients with CTD-ILD, requiring consideration of various clinical and radiological factors (figure 2) [116].

Systemic sclerosis-associated interstitial lung disease

The reported prevalence of SSc-ILD varies according to the definition used and ranges between 22% and 87%, with a pooled estimate of 47% [7]. While the radiological nonspecific interstitial pneumonia (NSIP) pattern is observed in the vast majority of patients with SSc-ILD, 19% of patients can present with the radiological UIP pattern, which portends a fibrosis-predominant process [7]. Substantial heterogeneity in disease trajectories and treatment responses exists within this previously seemingly homogeneous patient population [113, 117]. The 2024 American Thoracic Society clinical practice guidelines for treatment of SSc-ILD recommend mycophenolate, with cyclophosphamide, rituximab, tocilizumab and nintedanib suggested as alternative options [118]. By integrating guideline recommendations with RCT trial eligibility and the latest knowledge on phenotyping of SSc-ILD, we propose a stratified pharmacotherapeutic approach targeting inflammation-predominant, fibrosis-predominant and mixed inflammatory/fibrotic diseases (figure 3).

For patients with inflammation-predominant SSc-ILD, immunosuppressive drugs play a central role in disease management, with mycophenolate the commonly preferred first-line treatment option given its efficacy and safety profile [8, 118]. In addition to similarly improved FVC and dyspnoea severity with

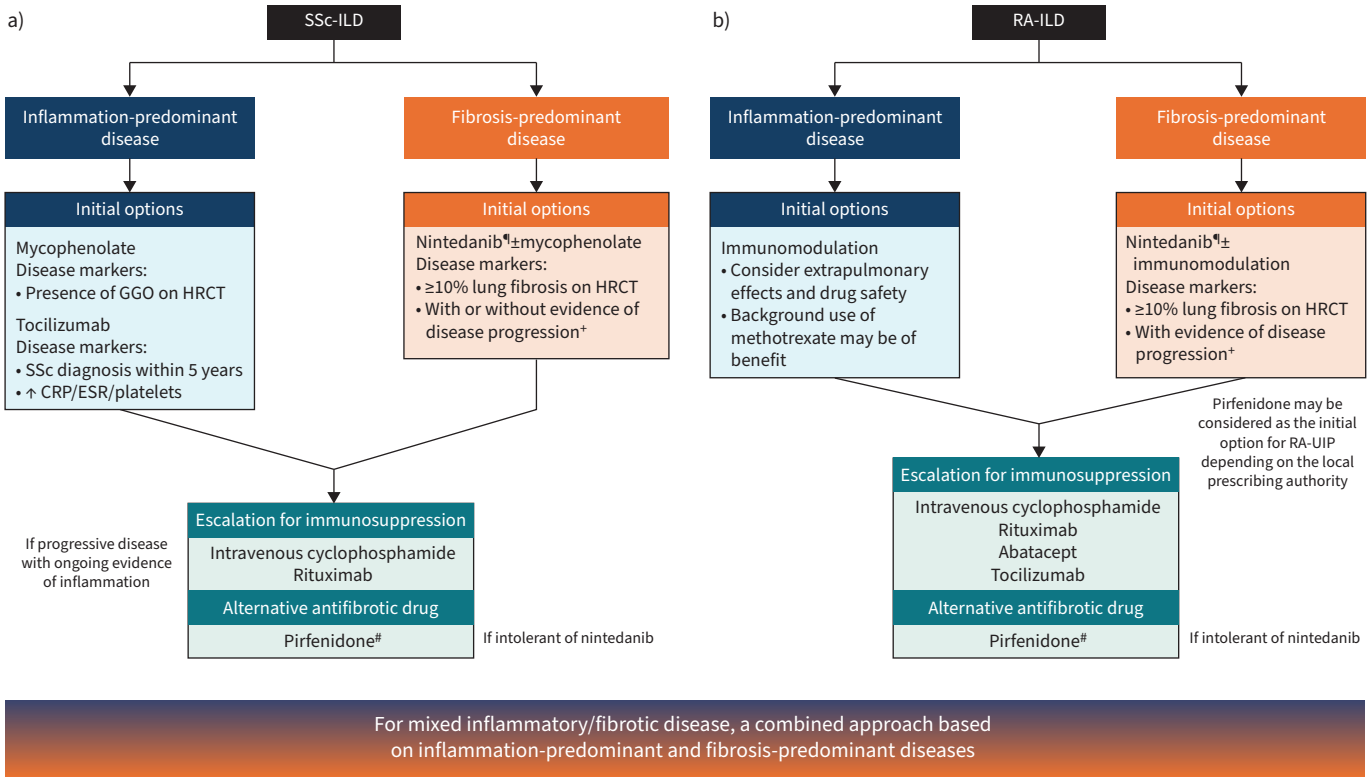

FIGURE 3 Proposed immunosuppressive and antifibrotic pharmacotherapeutic approach for a) systemic sclerosis-associated interstitial lung disease (SSc-ILD) and b) rheumatoid arthritis-associated lung disease (RA-ILD). CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GGO: ground-glass opacification; HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia. #: individual patient factors and regional differences in accessing different drugs should be considered; ¶: note that efficacy of nintedanib has been studied in patients with SSc-ILD with and without disease progression [119, 120], but only in patients with RA-ILD with disease progression and not as the first-line therapy prior [120]; +: different criteria have been proposed to define disease progression, which include a combination of clinical symptoms, physiological impairment measured by lung function, and/or radiological changes on HRCT [13, 120, 121].

mycophenolate compared to cyclophosphamide [122, 123], mycophenolate has a superior drug-related adverse event profile, with high patient tolerance supported by both clinical trial and real-world data [122, 124]. An important consideration of the alternative first-line treatment option for patients with inflammation-predominant SSc-ILD is the use of tocilizumab in those with early inflammatory disease, given its efficacy on FVC stabilisation as described previously [8]. Both cyclophosphamide and rituximab improve FVC in patients with SSc-ILD and moderate-to-severe lung function impairment or progressive disease, including in those who have experienced treatment failure using other immunosuppressive drugs, with potential beneficial effects on dyspnoea and health-related quality of life for cyclophosphamide [8, 125, 126]. Little high-quality evidence exists to guide the choice between cyclophosphamide and rituximab, and there are several influencing factors to consider. Access to rituximab and its high cost are known to be important barriers to its use in other diseases such as lymphoproliferative disorders [127], although the emergence of biosimilars may address these. Differences in adverse drug event profiles exist between the two agents. Rituximab is preferred for patients of child-bearing age, given the risk of infertility with cyclophosphamide. A head-to-head comparison in the RECITAL trial of a mixed group of patients with CTD-ILD showed that patients receiving rituximab had fewer drug-related adverse events than those receiving cyclophosphamide [128].

In patients with fibrotic SSc-ILD with and without evidence of disease progression, nintedanib, either as a single agent or in combination with mycophenolate, reduces lung function decline (table 1) [119, 120, 142]. The efficacy of pirfenidone has only been evaluated as a sole treatment in a pilot trial of 34 patients with SSc-ILD, which was further limited by the vast majority (94%) receiving subtherapeutic doses of pirfenidone [143]. Fewer than 10 patients with SSc-ILD were included in the RELIEF trial of progressive pulmonary fibrosis of different ILD subtypes, which reported that pirfenidone potentially attenuates FVC decline based on imputation following premature trial termination due to slow recruitment [121]. The Scleroderma Lung Study III trial intended to compare the therapeutic efficacy of combined mycophenolate and pirfenidone with mycophenolate alone in 150 patients with SSc-ILD, but was terminated after reaching only one third of the target sample size [141]. Similar FVC improvement has also been observed for combined therapies and for mycophenolate alone at 18 months, although there was a more rapid change at 6 months with combined therapies [73]. Dyspnoea severity and health-related quality of life showed comparable improvements with both interventions, although it is difficult to draw concrete conclusions due to the study limitation of inadequate power.

Pharmacotherapies for patients with mixed inflammatory/fibrotic SSc-ILD based on clinical and radiological assessments have not been specifically evaluated in clinical trials. Nevertheless, patients of this phenotype are likely to have been included in existing RCTs of immunosuppressive and antifibrotic drugs, which implies the relevance of combining the aforementioned approaches for treating patients with inflammation-predominant and fibrosis-predominant SSc-ILD. However, the order of initiation and escalation of immunosuppressive and antifibrotic drugs in patients with mixed inflammatory/fibrotic SSc-ILD is uncertain. Despite overlapping potential side effects with gastrointestinal symptoms and liver function derangement between immunosuppressive and antifibrotic drugs, their combined use appears to have acceptable safety profiles in clinical trials [119, 141, 139]. Of note, patients with very severe lung function impairment with a FVC of <45% predicted or diffusing capacity of the lungs for carbon monoxide of <40% predicted are often excluded from existing RCTs of SSc-ILD.

Rheumatoid arthritis-associated interstitial lung disease

While ILD affects patients with RA less commonly than those with SSc, it is not rare, with reported prevalence ranging between 1% and 31% and a pooled estimate of 11% [7]. Up to 52% of patients with RA-ILD experience disease progression [144, 145]. The UIP pattern is the most common radiological pattern in patients with RA-ILD, which portends a progressive disease course and high mortality [145–148]. Still, a substantial number of patients with RA-ILD have non-UIP radiological patterns such as NSIP and organising pneumonia [7]. Thus, both immunosuppressive and antifibrotic drugs should be considered in patients with RA-ILD, although targeting fibrosis is likely to be crucial compared to other CTD-ILDs (figure 3). It is noteworthy that heavy immunosuppression during stable disease or acute exacerbation increases mortality risk in patients with IPF, which has the pathognomonic feature of radiological UIP pattern as also seen in some patients with RA-ILD [149, 150]. Nevertheless, higher serum C-reactive protein levels are independently associated with reduced 5-year survival in patients with RA-ILD, as seen those with SSc-ILD [151]. There is also a need to take into consideration the extrapulmonary manifestations of RA.

No RCTs have evaluated the use of immunosuppressive drugs in RA-ILD, with only three studying antifibrotic drugs (table 2) [121, 140, 153]. As such, the pharmacotherapy approach proposed for

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TABLE 1 Key phase 2 and 3 randomised controlled trials of immunosuppressive and antifibrotic drugs for SSc-ILD

Author/Trial	Interventions	Participants (n)	Disease characteristics	Efficacy end-points					
				FVC	D_{LCO}	Survival	HRQoL	Dyspnoea	CT changes
Immunosuppressive drugs									
Hoyles 2006 [129]	Active group: 20 mg prednisolone on alternate days plus 6× monthly cyclophosphamide infusion (600 mg·m^{-2}·month^{-1}) followed by azathioprine (2.5 mg·kg^{-1}·day^{-1}) for 6 months Comparator: placebo for 12 months	45	SSc disease duration: both incident and prevalent cases with no duration limit ILD disease duration: not prespecified (median: 4 months for both, range 1–59 months) Lung function: not prespecified (mean FVC: 80–81% pred, mean D_{LCO}: 53–55% pred) Extent of lung involvement: not prespecified (mean: 19–20%, range 5–40%) Symptoms: not prespecified Other: NA	✓	x	NA	NA	x	x
SLS-1 [130–133]	Active group: oral cyclophosphamide (2 mg·m^{-2}·day^{-1}) for 12 months Comparator: placebo for 12 months	158	SSc disease duration: within 7 years ILD disease duration: NA Lung function: FVC 45–85% pred Extent of lung involvement: any GGO Symptoms: grade 2 exertional dyspnoea of the Mahler Dyspnea Index Other: BAL neutrophilia and/or eosinophilia or HRCT GGO	✓✓[#]	x	x	x	✓✓	✓✓
SLS-II [122, 133–135]	Active group: oral mycophenolate (target dose 1.5 g twice daily) for 24 months Comparator: oral cyclophosphamide (2 mg·kg^{-1}·day^{-1}) for 12 months, followed by placebo for 12 months	142	SSc disease duration: within 7 years ILD disease duration: NA Lung function: FVC 45–<80% pred, D_{LCO} ⩾40% pred Extent of lung involvement: any GGO with or without reticulation Symptoms: ⩾Grade 2 exertional dyspnoea of the Mahler Dyspnea Index Other: NA	x[¶]	x	x	NA	x[¶]	x[¶]
faSScinate [95]	Active group: subcutaneous tocilizumab 162 mg weekly for 48 weeks Comparator: placebo for 48 weeks	87	SSc disease duration: within 5 years ILD disease duration: NA Lung function: not prespecified (mean FVC: 80–82% pred, mean D_{LCO}: 73–74% pred) Extent of lung involvement: NA Symptoms: NA Other: active progressive disease of <1 year duration based on skin manifestation or tendon friction rub +elevated acute-phase reactant levels (CRP/ESR/platelets)	✓✓	x	x	x	x	NA
Sircar 2018 [136]	Active group: rituximab 1000 mg at Day 0 and 15, followed by 6 monthly Comparator: intravenous cyclophosphamide (500 mg·m^{-2}) monthly for 6 months, followed by azathioprine or mycophenolate	60	SSc disease duration: within 3 years ILD disease duration: NA Lung function: FVC 45–<80% pred Extent of lung involvement: NA Symptoms: New York Heart Association Class II and III Other: NA	✓✓	NA	x	NA	NA	NA

Continued

TABLE 1 Continued

Author/Trial	Interventions	Participants (n)	Disease characteristics	Efficacy end-points					
				FVC	D_{LCO}	Survival	HRQoL	Dyspnoea	CT changes
focuSSced [96]	Active group: subcutaneous tocilizumab 162 mg weekly for 48 weeks Comparator: placebo for 48 weeks	210	SSc disease duration: within 5 years ILD disease duration: NA Lung function: FVC >55% pred, D_{LCO} >45% pred Extent of lung involvement: not prespecified (83% had >20% lung involvement) Symptoms: NA Other: active disease of ⩽18 months based on skin manifestation or tendon friction rub+elevated acute-phase reactant levels (CRP/ESR/platelets)	✓✓	x	x	x	NA	✓✓
DESIRES [137]	Active group: rituximab (375 mg·m^{-2}) weekly for 4 weeks Comparator: placebo for 4 weeks Follow-up at 24 weeks	56	SSc disease duration: NA ILD disease duration: NA Lung function: vital capacity ⩾60% pred, D_{LCO} ⩾40% pred Extent of lung involvement: NA Symptoms: NA Other: NA	✓✓	x	x	x	NA	✓✓
RECITAL [128]	Active group: rituximab 1000 mg at Day 0 and 14 Comparator: intravenous cyclophosphamide (600 mg·m^{-2}) monthly for 6 months Additional immunosuppressive drugs were allowed from Week 24	97 with different CTD-ILDs (39 SSc-ILD)	CTD disease duration: NA ILD disease duration: NA Lung function: NA (mean FVC: 68–71% pred, mean D_{LCO}: 40% pred) Extent of lung involvement: NA Symptoms: NA Other: severe or progressive ILD	x[¶]	x	x	x[¶]	NA	NA
EVER-ILD [138]	Active group: rituximab 1000 mg at Day 1 and 15 with oral mycophenolate 2 g daily for 6 months Comparator: placebo with oral mycophenolate 2 g daily for 6 months Additional immunosuppressive drugs were allowed from Week 24	122 with NSIP pathological or HRCT pattern (23 SSc-ILD)	CTD disease duration: NA ILD disease duration: NA Lung function: NA (mean FVC: 67–70% pred, mean D_{LCO}: 30–40% pred) Extent of lung involvement: NA Symptoms: NA Other: did not respond or relapsed after a first-line of glucocorticoids and/or immunosuppressive treatment, which was defined as decrease or increment of <10% pred in FVC compared to before treatment over a period of 6–12 months	✓✓	x	✓✓	x	x	x
Antifibrotic drugs									
LOTUSS [139]	Active group: pirfenidone 801 mg three times daily with 2-week titration for 16 weeks Comparator: pirfenidone 801 mg three times daily with 4-week titration for 16 weeks	62	SSc disease duration: <7 years ILD disease duration: within 2 years Lung function: FVC ⩾50% pred, D_{LCO} ⩾40% pred Extent of lung involvement: NA Symptoms: NA Other: NA	x	x	x	x	x	NA

Continued

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TABLE 1 Continued

Author/Trial	Interventions	Participants (n)	Disease characteristics	Efficacy end-points					
				FVC	D_{LCO}	Survival	HRQoL	Dyspnoea	CT changes
SENCSIS [119]	Active group: nintedanib 150 mg twice daily for 52 weeks Comparator: placebo for 52 weeks	576	SSc disease duration: within 7 years ILD disease duration: NA Lung function: FVC ⩾40% pred, D_{LCO} 30–89% pred Extent of lung involvement: ⩾10% with fibrosis Symptoms: NA Other: NA	✓✓	x	x	x	x	NA
INBUILD (*post hoc* analyses) [120, 140]	Active group: nintedanib 150 mg twice daily for 52 weeks Comparator: placebo for 52 weeks	97 with different CTD-ILDs (37 SSc-ILD)	CTD disease duration: NA ILD disease duration: NA Lung function: FVC ⩾45% pred, D_{LCO} 30–<80% pred Extent of lung involvement: >10% with fibrosis Symptoms: NA Other: disease progression defined as relative FVC decline ⩾10% pred or a combination of ⩾2 of the following criteria over 2 years despite standard therapy: relative FVC decline ⩾5–<10% pred, worsening symptoms or imaging progression	✓✓	NA	x	x	NA	NA
RELIEF [121]	Active group: pirfenidone 801 mg three times daily for 48 weeks Comparator: placebo for 48 weeks	127 with different ILDs (8 SSc-ILD)	CTD disease duration: NA ILD disease duration: ⩾9 months Lung function: FVC 40–90% pred, D_{LCO} 10–90% pred Extent of lung involvement: >10% with fibrosis Symptoms: NA Other: disease progression defined as annual FVC decline ⩾5% pred based on ⩾3 FVC measurements within 6–24 months despite standard therapy	✓✓	✓✓	x	x	NA	NA
SLS-III [141]	Active group: oral mycophenolate (target dose 1.5 g twice daily)+pirfenidone 801 mg three times daily for 18 months Comparator: oral mycophenolate (target dose 1.5 g twice daily) for 18 months	51	SSc disease duration: within 7 years ILD disease duration: NA Lung function: FVC ⩽85% pred, D_{LCO} ⩾30% pred (with exclusion of clinically significant or untreated mild PH, if D_{LCO} 30–40%) Extent of lung involvement: any GGO Symptoms: ⩾grade 2 exertional dyspnoea of the Mahler Dyspnea Index Other: NA	x[¶]	NA	x	x[¶]	x[¶]	x

Grey colour indicates results from patient cohorts inclusive of non-SSc-ILD. ✓: non-statistically significant positive effects for the active group; ✓✓: statistically significant positive effects for the active group; **x**: no between-group difference; BAL: bronchoalveolar lavage; CRP: C-reactive protein; CT: computed tomography; CTD: connective tissue disease; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; GGO: ground-glass opacification; HRCT: high-resolution computed tomography; HRQoL: health-related quality of life; ILD: interstitial lung disease; NA: not applicable; NSIP: nonspecific interstitial pneumonia; PH: pulmonary hypertension; SSc: systemic sclerosis. [#]: assessment at 24 months showed similar results favouring cyclophosphamide; [¶]: improvements noted for both active group and comparator with no significant between-group differences.

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TABLE 2 Randomised controlled trials of antifibrotic drugs for RA-ILD

Trial	Interventions	Participants (n)	Disease characteristics	Efficacy end-points					
				FVC	D_{LCO}	Survival	HRQoL	Dyspnoea	CT changes
RELIEF [121]	Active group: pirfenidone 801 mg three times daily for 48 weeks Comparator: placebo for 48 weeks	127 with different ILDs (17 RA-ILD)	CTD disease duration: NA ILD disease duration: ⩾9 months Lung function: FVC 40–90% predicted, D_{LCO} 10–90% pred Extent of lung involvement: >10% with fibrosis Symptoms: NA Other: disease progression defined as annual FVC decline ⩾5% pred based on ⩾3 FVC measurements within 6–24 months despite standard therapy	✓✓	✓✓	x	x	NA	NA
INBUILD *post hoc* analyses [120, 152]	Active group: nintedanib 150 mg twice daily for 52 weeks Comparator: placebo for 52 weeks	89 RA-ILD	RA disease duration: NA ILD disease duration: NA Lung function: FVC ⩾45% pred, D_{LCO} 30–<80% pred Extent of lung involvement: >10% with fibrosis Symptoms: NA Other: disease progression defined as relative FVC decline ⩾10% pred or a combination of ⩾2 of the following criteria over 2 years despite standard therapy: relative FVC decline ⩾5–<10% pred, worsening symptoms or imaging progression	✓✓	NA	x	x	NA	NA
TRAIL1 [153]	Active group: Pirfenidone 801 mg three times daily for 52 weeks Comparator: Placebo for 52 weeks	231	RA disease duration: NA ILD disease duration: NA Lung function: FVC ⩾40% pred, D_{LCO} ⩾30% pred Extent of lung involvement: >10% with fibrosis Symptoms: NA Other: NA	✓✓	NA	x	NA	x	NA

Grey colour indicates results from patient cohorts inclusive of non-RA-ILD. ✓: non-statistically significant positive effects for the active group; ✓✓: statistically significant positive effects for the active group; **x**: no between-group difference; CT: computed tomography; CTD: connective tissue disease; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; HRQoL: health-related quality of life; ILD: interstitial lung disease; NA: not applicable; RA: rheumatoid arthritis.

inflammation-predominant SSc-ILD may be extrapolated to patients with RA-ILD of similar nature. Observational studies in patients with RA-ILD provide some corroborating evidence on mycophenolate [154, 155] and tocilizumab [156] in stabilising or improving lung function, with the use of cyclophosphamide associated with better survival [157]. For patients with progressive RA-ILD for whom conventional DMARDs fail to manage articular manifestations, rituximab [158] and abatacept [159–161], a selective costimulation modulator, appear to stabilise lung function, respiratory symptoms and radiological changes. Similar potential therapeutic benefits with Janus kinase inhibitors such as tofacitinib and baricitinib have been suggested from recent uncontrolled data in patients with RA-ILD [162, 163]. Tofacitinib has also been reported in case series, with potential benefits for patients with other CTD-ILDs, particularly anti-melanoma differentiation-associated protein 5 antibody-positive dermatomyositis [164–166]. Given the observed negative impact of immunosuppressive drugs in IPF [149], there has been caution with their use in RA-ILD with UIP pattern [8]. Of note, patients included in observational studies of RA-ILD had varying radiological patterns, including both UIP and non-UIP patterns, suggesting a potential indication for immunosuppressive drugs in patients with RA-ILD irrespective of the phenotypes.

Telomere length measurements may inform risks associated with immunosuppression in patients with ILD [167], although the availability and cost of testing vary geographically [53, 168].

Apart from the aforementioned RELIEF trial of progressive pulmonary fibrosis that included 17 patients with RA-ILD [121], pirfenidone has been studied in the phase 2 TRAIL1 trial in patients with RA-ILD [153]. This trial was underpowered owing to early termination as a result of slow recruitment and the COVID-19 pandemic. While the composite primary end-point of ⩾10% FVC decline or death was not met, patients with a radiological UIP pattern receiving pirfenidone had slower annual decline in FVC compared to those receiving placebo. In the *post hoc* subgroup analyses of the INBUILD trial of progressive pulmonary fibrosis, patients with RA-ILD demonstrated reduced FVC decline with nintedanib, as seen in the primary analyses of the overall study population [152]. Nevertheless, no effects on respiratory symptoms or health-related quality of life were noted in either RCT. Together, these findings demonstrate therapeutic benefits of antifibrotic drugs for slowing disease progression in patients with fibrotic and mixed inflammatory/fibrotic RA-ILD.

Conclusion

This newly proposed pharmacotherapeutic approach based on the concept of preventative medicine provides a framework for research development and subsequent clinical practice of goal-focused treatments at different disease stages of CTD-ILD, which extends beyond symptomatic patients. However, it is important to acknowledge the heterogeneous disease trajectories of CTD-ILDs and treatment decisions need to be personalised, taking into account individual patient characteristics and disease risk factors. As we currently stand, there are some major gaps that need to be addressed. First, the precise disease mechanisms of CTD-ILDs remain elusive. This is important for identifying clinically applicable biomarkers for early diagnosis and prognostication for different disease stages of CTD-ILD, as well as therapeutic targets for drug development. Advances with integrative multi-omics analyses of genomics, transcriptomics, proteomics and metabolomics, as well as quantitative analyses of HRCT for lung parenchymal changes and extents, provide a platform for advancement. Second, there are few clinical trials of pharmacotherapies in patients with different CTD-ILDs. While registry-based observational studies can be informative in providing insights into long-term treatment responses, randomised controlled clinical trials are needed to provide high-quality evidence to inform treatment guidance, particularly for changing clinical practice. Novel clinical trial designs, such as pragmatic and basket trial designs, may allow for efficient trial accrual. Third, the ideal approach and cost-effectiveness of integrating immunosuppressive and antifibrotic drugs into CTD-ILD therapy needs to be evaluated. Access to antifibrotic drugs also varies geographically and the high costs for some patients requires attention [169, 170]. Of note, non-pharmacological interventions, such as smoking cessation and vaccinations for respiratory infection [171], may play a role in altering the development and progression of ILD, as well as preventing acute exacerbation with limited proven efficacious therapies. There is also emerging data on the potential role of lung ultrasound in detecting ILD in patients with CTD [172], which provides an alternative approach that may be more accessible in some regions. Moving forward, close interdisciplinary collaboration of respiratory medicine and rheumatology is needed to establish risk stratification and therapeutic options for different stages of CTD-ILD.

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