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REVIEW

Management of progressive pulmonary fibrosis associated with connective tissue disease

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ABSTRACT

Introduction: Fibrotic interstitial lung disease (ILD) is a frequent and severe complication of connective tissue disease (CTD).

Areas covered: In this narrative review, we update the most relevant differential characteristics of fibrotic ILD associated with CTD (CTD-ILD) and propose a diagnostic and therapeutic approach based on a review of the articles published between 2002 and 2022 through PubMed.

Expert opinion: The subset of ILD, mainly the radiological/histological pattern and the degree of fibrotic component, usually determines the prognosis and therapeutic strategy for these patients. Some patients with CTD-ILD can develop progressive pulmonary fibrosis (PPF) with severe deterioration of lung function, rapid progression to chronic respiratory failure, and high mortality. PPF has been described in many CTDs, mainly in systemic sclerosis and rheumatoid arthritis, and requires a multidisciplinary diagnostic and therapeutic approach to improve patient outcomes.

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Interstitial lung disease; connective tissue disease; progressive pulmonary fibrosis; multidisciplinary consultation; diagnosis; treatment

1. Introduction

Interstitial lung disease (ILD) has been described in almost all connective tissue diseases (CTDs) [1–12], with higher prevalence in systemic sclerosis (SSc) [2,3], rheumatoid arthritis (RA) [4,5], and in some groups of inflammatory myositis (dermatomyositis, antisynthetase syndrome, and overlap syndromes) [6–9].

The pathogenesis of ILD associated with CTD (CTD-ILD) is not completely elucidated, although the main hypothesis assumes that tissue fibrosis is preceded by an immune-mediate process [1–6,13–16]. In SSc, this process seems to be triggered by endothelial injury in the context of encompassing immune activity [3,14,15]. In the last decades, some research studies have suggested different pathways to be implicated in the development of ILD in SSc and RA, including immune-mediated alveolar epithelial damage and endothelial disorders, and the subsequent and progressive abnormal extracellular matrix remodeling and myofibroblast formation [17]. Following the identification of these pathogenic pathways and implicated mediators, different future potential strategies are being pre-clinically evaluated in SSc-associated ILD (SSc-ILD) and RA-associated ILD (RA-ILD), including the regulation of some relevant overexpressed extracellular matrix proteins such as COL5A2 [18,19].

The clinical course of CTD-ILD is variable, but patients with evidence of pulmonary fibrosis tend to have a worse prognosis. A proportion of fibrotic CTD-ILD patients will develop progressive pulmonary fibrosis (PPF) and rapid deterioration of pulmonary function tests (PFTs), leading to end-stage respiratory failure and high mortality [13,20–23]. Moreover, it has been described that fibrotic ILD is characterized by an increased distal alveolar bacterial burden that might be responsible for both a rapidly deteriorating course of fibrotic disease and deadly exacerbations [24,25]. It has also been shown, that RA-ILD has a higher serious infections risk, especially pneumonia [26,27].

The diagnosis of fibrotic CTD-ILD, especially the early identification of patients with PPF, is complex. In these cases, a comprehensive assessment is essential, including accurate staging of the severity of the disease and extrapulmonary manifestations. In addition, an individualized and comprehensive therapeutic approach is important in the treatment of CTD-ILD to control the autoimmune and inflammatory activity of the underlying disease and to prevent, when necessary, the progression of fibrotic pulmonary changes [28]. For all these reasons, a multidisciplinary approach is worthwhile in the treatment of the different stages in CTD-ILD, for diagnosis and treatment (both initial and during follow-up) [29].

The aim of this article is to describe the most relevant differential characteristics of PPF in CTD and to propose a diagnostic and therapeutic approach based on the published evidence and the clinical experience of

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Article highlights

- Interstitial lung disease (ILD) is a frequent and severe complication of connective tissue diseases (CTD), such as systemic sclerosis and rheumatoid arthritis.
- The diagnosis of fibrotic ILD in CTDs, especially the early identification of patients with progressive pulmonary fibrosis, is complex, requiring a comprehensive assessment, including accurate staging of the disease severity and extrapulmonary manifestations.
- An individualized and comprehensive therapeutic approach is important in the treatment of ILD associated with CTD to control the autoimmune and inflammatory activity of the underlying disease and to prevent, when necessary, the progression of fibrotic pulmonary changes.
- A multidisciplinary diagnostic and therapeutic approach is required to not only guarantee early diagnosis but also provide comprehensive and individualized treatment.
- Antifibrotic drugs, such as nintedanib, have been shown in recent clinical trials to attenuate progressive pulmonary fibrosis in patients with CTD and may provide therapeutic benefit.

a multidisciplinary group of experts. Narrative literature review (PubMed Central) was used to search for the articles published between 2002 and 2022, excluding clinical cases. The terms 'interstitial lung disease', 'progressive fibrosis', and 'connective tissue disease' were used in the literature search.

2. Identification and diagnosis of CTD-ILD

ILD may present as a complication during the course of a known CTD or the clinical onset of a CTD. In both scenarios, a multidisciplinary diagnostic and therapeutic approach is ideally advised [29–31].

In patients with a known CTD, this multidisciplinary model of care has been shown to reduce the time to ILD identification, as well as the time between diagnosis and initiation of treatment [29]. In addition, assessing the severity of the ILD and associated extrapulmonary manifestations is essential for decision making [29].

In patients with new-onset ILD, multidisciplinary assessment allows a specific diagnosis to be established in up to 80.5% of cases [17,29–33]. But, most importantly, it allows early identification of patients with an autoimmune pathogenic substrate, either by reaching the diagnosis of a definite CTD or by establishing the initial orientation of interstitial pneumonia with autoimmune features (IPAF), which has prognostic and therapeutic implications [30,31,34,35].

The recommended composition of a multidisciplinary committee in CTD-ILD should not only include expert ILD pulmonologists, radiologists, and pathologists, but also include experts in CTD (rheumatologists) [31,32].

Notably in CTD, some ILD may be subclinical until advanced stages and the detection of ILD is frequently performed with months or even years of delay [1–12], particularly in RA [4,5,16,36,37]. Increasing data suggest that the diagnostic delay associate a poor outcome and that ILD identification can influence the therapeutic approach [17,29–35]. Therefore, the early detection of this complication is essential. Addressing this concern, regularly monitoring respiratory symptoms and auscultation is essential; 'velcro-type' crackles to lung auscultation, correlates very well with the presence of pulmonary fibrosis [38]. Clinically, ILD presents with repetitive dry cough and exertional dyspnea, which may progress to respiratory failure.

Table 1 lists those patient features that can help to identify fibrotic CTD-ILD patients [17,29–31,35,39]. In case of suspected ILD, a chest X-ray and PFTs including spirometry and carbon monoxide diffusing capacity (DLCO) are usually performed for initial screening. However, chest X-ray is a technique with low sensitivity in the early stages, when only high-resolution computed tomography (HRCT) detects the mild interstitial changes, being the most sensitive imaging tool to detect ILD. The PFTs in fibrotic ILD show a restrictive ventilatory (decrease of total lung capacity [TLC] and forced vital capacity [FVC]) pattern together with a decrease in DLCO. However, in early stages, a decrease in DLCO with preserved FVC may be found. Furthermore, if only a DLCO decrease is present or the severity of DLCO decrease is not associated with a TLC or FVC decline, pulmonary arterial hypertension (PAH) should be considered, especially in SSc patients

To confirm ILD and to characterize its pattern, the chest HRCT is essential. Due to the HRCT radiologic-histologic correlation pattern and the association of CTD as a cause of ILD, lung biopsy is not usually required. HRCT is also useful to

Table 1. Patient features and invasive and noninvasive tests useful for identifying an ILD in a CTD.

Noninvasive tests

Patient history:
- Smoking
- Medication use
- Environmental exposures (mold, feathers, animals, metal dusts, wood dusts, plant dusts, livestock, stone polishing, and cutting)
- Current or recent occupations (e.g. hairdressing) and current or recent hobbies
- Family history of ILD

Pulmonary function tests:
- FVC
- DLCO
- If possible, total lung capacity

Autoantibodies associated with an increased risk of developing ILD:
- Anti-cyclic citrullinated peptide at high titers
- Anti-Scl 70
- Anti-Jo1, PL-7 and PL-12
- Anti-Ro (SSA)
- Anti-MDA 5
- Anti-PM/Scl
- Anti-Th/To

Imaging tests
- HRCT: reticulation, bronchiectasis and traction bronchiectasis, 'honeycombing' pattern, 'ground glass'.

Invasive tests

Bronchoalveolar lavage, transbronchial criobiopsy
Lung biopsy

CTD, connective tissue disease; DLCO, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease.

Table 2. Radiological patterns and signs of fibrosis on chest HRCT [40].

Radiological patterns	Radiological signs
Linear-reticular pattern	• Thickening of the intralobular septa: produces linear images of several centimeters in length. • Intralobular interstitial thickening: presence of a fine reticular meshwork extending from the peribronchovascular structures of the center of the lobule to the interlobular septa, with a 'spider web' morphology.
Nodular pattern	• Small nodules: > 2 mm • Miliary nodules: 1–2 mm
Ground-glass pattern	• Faint increase in lung density often geographically distributed, which does not obliterate adjacent vascular structures
Cystic pattern	• Thin-walled rounded images (generally 1 to 3 mm thick), well-defined and with air inside them
Condensation or consolidation pattern	• Increased pulmonary attenuation associated with blurring of adjacent vessel contours
Usual interstitial pneumonia (UIP)	• Subpleural, basal and symmetrical localization; occasionally diffuse • Apico-basal progression' • Ground-glass' (minimal)Reticulation, bronchiectasis and traction bronchiectasis' • Honeycombing' pattern
Nonspecific interstitial pneumonia (NSIP) Nonspecific interstitial pneumonia (NSIP) fibrotic*	• Variable involvement (central and peripheral) • Preference in inferior lobes • Patchy 'ground-glass' opacities associated with linear, reticular and micronodular images • Traction bronchiectasis/bronchilectasis* • Infrequent 'honeycombing' pattern

*Traction bronchiectasis/bronchilectasis refers to NSIP fibrotic.

Table 3. SER-SEPAR proposed screening criteria for diffuse interstitial lung disease in patients diagnosed with rheumatoid arthritis [44].

The following 3 clinical situations are to be screened for ILD:

(1) Patients with respiratory symptoms (cough and/or dyspnea) of more than 3 months of evolution.
(2) Patients in whom velcro-type crackles are detected in respiratory auscultation, even if they are asymptomatic.
(3) In patients without respiratory symptoms and with normal respiratory auscultation, screening will be done according to the score obtained based on the number of risk factors present for the development of this complication.

Any patient scoring ≥ 5 points will be considered eligible for screening:

Set of variables and proposed score for each of the variables for the overall score	**Score**
• Age ≥ 60 years	2
• Male sex	1
• History of smoking (active smoker or former smoker)	
• ≤ 20 packs/year: 2 points	2
• > 20 packs/year: 3 points	3
• Duration of disease > 5 years	1
• Persistently moderately-high activity: Average DAS28-VSG > 3.2 since disease diagnosis in baseline RA (time since diagnosis ≤ 12 months) or DAS28-VSG > 3.2 for a minimum of 6 months in established RA	1
• Serology (only the criterion with the highest weighting is counted toward the total score)	
• RF positive > 3 times above ULN	1
• ACPA positive ≤ 3 times the ULN	2
• ACPA positive > 3 times the ULN	3
• Family history of ILD	1

ACPA: anti-cyclic citrullinated peptide antibodies; ILD: interstitial lung disease; RA: rheumatoid arthritis; RF: rheumatoid factor; SEPAR: Spanish Society of Pneumology and Thoracic Surgery; SER: Spanish Society of Rheumatology; ULN: upper limit of normal.

quantify the extent of parenchymal involvement, the type of interstitial changes (predominant fibrotic or ground-glass) and pattern (usual interstitial pneumonia [UIP] vs. non-UIP), and to assess the disease progression. Table 2 shows the radiological patterns and signs of fibrosis on chest HRCT [40].

Bronchoalveolar lavage would be recommended depending on the clinical context; to rule out infections or to better approach a potential differential diagnosis (if relevant exposures for ILD development are present). Lung biopsy should be reserved for cases in which other conditions, such as hypersensitivity pneumonitis,pneumoconiosis, or malignancies, may be present in a patient with CTD [17,28,32].

PFTs (FVC, TLC and DLCO), 6-minutes walking test (6MWT), and quality of life (QoL) questionnaires are used for monitoring ILD progression. HRCT is recommended during the follow-up in cases that present clinical and/or PFTs worsening, to differentiate disease progression versus acute exacerbation or other respiratory complications such as lung cancer or respiratory infection. In patients with advanced stages of their disease, or in cases with very severe DLCO decline and marked oxyhemoglobin desaturation with exercise, Doppler echocardiography is also useful to detect the development of associated PAH.

Although ILD is a complication described in many CTDs, the prevalence is higher in SSc and RA. The prevalence of ILD ranges from 30% to 60% in SSc, and progressive pulmonary fibrosis is the leading cause of death [41]. The most prevalent fibrotic histologic pattern is nonspecific interstitial pneumonia (NSIP) [2,3,42]. Systematic screening for ILD is recommended in all patients at diagnosis of SSc and, subsequently, on an annual basis during follow-up based on its frequency and mortality [2,3,14,20]. For screening, HRCT is recommended at diagnosis of the disease, since it has been shown that initial screening by PFT has a non-negligible percentage of false negatives [43].

In RA, the prevalence of symptomatic ILD diagnosed by chest HRCT varies from 10% to 29%, being the second cause of death after cardiovascular complications [4,5,16]. The radiological UIP pattern has been more frequently described than NSIP [4,5,16]. Despite a frequent and serious complication, no recommendations on RA-ILD screening have been published until now. In order to respond to this clinical need, a joint collaboration between the Spanish societies of Rheumatology (SER) and Pneumology and Thoracic Surgery (SEPAR) have recently developed a multidisciplinary proposal of selective screening criteria shown in Table 3 [44]. The main risk factors for ILD development in SSc and RA are shown in Table 4.

Table 4. Main risk factors for ILD development in SSc and RA, and prognostic factors for mortality and progression of ILD.

Systemic sclerosis

Risk factors for ILD development

- Male gender
- African-American or Asian ethnicity
- Diffuse skin involvement
- Cardiac involvement
- Anti-Scl 70 or topoisomerase I and anti-Th/To positivity

Variables associated with an increased risk of ILD progression

Demographic	• Male sex • Older age • African-American ethnicity • Smoking
Clinical	• Diffuse skin involvement with elevated Rodnan index scores at diagnosis of ILD • Poorly controlled gastroesophageal reflux disease • Presence of arthritis • Time of disease evolution (first 3 years)
Laboratory	• Elevated C-reactive protein • Anti-Scl 70 antibody positivity • Anti-RNA polymerase III antibody positivity • Elevated KL-6 levels
Pulmonary function tests	• Low basal FVC (< 70%) • Low basal DLCO not due to other causes (mainly pulmonary arterial hypertension) • Deterioration of FVC ≥ 10% during follow-up or fall in its values between 5% and 9% with a deterioration of DLCO ≥ 15%
HRCT	• Extent of fibrotic changes > 20%

Rheumatoid arthritis

Risk factors for ILD development

- Male sex
- Advanced age
- Late onset of the disease
- Duration of RA
- Smoking
- Moderate or high sustained RA activity according to DAS28 scores
- RF positive
- ACPA positive
- Antibodies directed against carbamylated proteins (anti-CarP)
- *MUC5B* gene mutations
- Mutations of telomerase genes leading to accelerated telomere shortening

Prognostic factors

Variables associated with ILD progression	• Radiologic pattern of UIP • Elevated ACPA titers • Degree of baseline DLCO deterioration (having been demonstrated with two cutoff points: DLCO < 45% and, in those patients with a progressive fibrosing phenotype, DLCO < 54%), decrease ≥ 10% in FVC during follow-up • Extensive pulmonary involvement on HRCT of the chest • Elevated serum levels of IL-6 and KL-6
Prognostic factors for mortality	• Advanced age at the time of diagnosis of ILD (> 60-65 years) • Male sex • Duration of RA (the longer the duration of disease at the time of ILD diagnosis, the higher the mortality) • Moderate or high disease activity as assessed by the DAS28-VSG index • UIP pattern* • FVC and/or low baseline DLCO • Decrease in FVC >10% or DLCO >15% during follow-up • Extensive lung involvement on HRCT of the chest (>20-30%) • Elevated serum levels of KL-6

ACPA, anti-cyclic citrullinated peptide antibodies; DLCO, carbon monoxide diffusion capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IL-6, interleukin-6; ILD, interstitial lung disease; KL-6, Krebs von den Lugen glycoprotein; RA, rheumatoid arthritis; RF, rheumatoid factor; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

*In some studies, the radiological pattern is no longer a predictor of mortality after adjustment for confounding variables in the different multivariate analysis models. The main prognostic factors are the degree of baseline deterioration in the pulmonary functional tests (FVC and DLCO) and the magnitude of its worsening during follow-up.

Finally, ILD can be the initial clinical presentation of a CTD. For example, in RA-ILD, ILD precedes joint manifestations by months or years in up to 10–14% of patients [45–47]. Therefore, a complete evaluation for the presence of a CTD, including serological autoimmunity study and physical exam, is recommended in all patients with new-onset ILD (Table 5) [48]. It is important to keep in mind that anti-Ro or SSA, anti-synthetase, and anti-Th/To antibodies may be positive, even if antinuclear antibodies are negative [29–31].

Repeating the autoimmunity study during the follow-up of ILD patients is relevant because approximately 10–25% of cases that are initially idiopathic evolve into a CTD by clinical-

Table 5. Panel of antibodies to be requested in the evaluation of an ILD to assess its possible association with a CTD.

In the initial evaluation of all patients
• Antinuclear antibodies (detection by indirect immunofluorescence)
• Rheumatoid factor and anti-cyclic citrullinated peptide antibodies (ACPA)
If rheumatoid arthritis is suspected
• Anti-citrullinated peptide antibody (ACPA)
• Rheumatoid factor
If systemic sclerosis is suspected
• Anti-Scl70/topoisomerase I
• Anti-U3RNP (anti-fibrillarin)
• Anti-centromere
• Anti-Th/To
• Anti-RNA polymerase III
• Anti-PM/Scl
• Anti-U1RNP
• Anti-Ku
• Anti-NOR 90
If inflammatory myopathy is suspected
• Anti-synthetase (Jo-1, PL-7, PL-12, EJ, OJ and KS)
• Anti-HMG-CoA reductase
• Anti-MDA5
• Anti-SAE
• Anti-Mi-2
• Anti-U1RNP
• Anti-NXP2
• Anti-PM/Scl75
• Anti-TIF1-γ
• Anti-PM/Scl100
• Anti-SRP
• Anti-Ku
If primary Sjögren's syndrome is suspected
• Anti-SSA/Ro60
• Anti-SSB/La
• Anti-TRIM21/Ro52
• Rheumatoid factor
If ANCA vasculitis is suspected*
• Anti-neutrophil cytoplasm antibody (ANCA)

HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; MDA5: melanoma differentiation-associated protein 5; NXP2: nuclear matrix protein 2; PM/Scl: polymyositis/scleroderma; RNP: ribonucleoprotein; SAE: small ubiquitin-related modifier-activating enzyme; SRP: signal recognition particle; SSA/Ro: Sjögren-specific antibody A; SSB/La: Sjögrens-specific antibody B; TRIM: Tripartite Motif Containing 21;TIF1-: transcriptional intermediary factor 1 gamma.

*10-11% of patients with idiopathic pulmonary fibrosis develop ANCA (anti-myeloperoxidase or anti-proteinase 3), in most cases in the absence of symptoms of systemic vasculitis [50,51].

onset or autoimmunity positivity (although there is no consensus on what should be the frequency of serial testing for CTD) [49–51].

3. Progressive pulmonary fibrosis associated with CTD

Different definitions of progressive pulmonary fibrosis have been used, based on expert consensus, definitions used in clinical trials, and recently the definition published in the recent international guide, based on functional, clinical, and radiological parameters [52]. The INBUILD randomized clinical trial [53] used the following criteria to define progression in patients with fibrosing ILD: 1) a decrease in baseline FVC >10%; 2) a decrease in FVC between 5–10% with evidence of fibrosing progression on HRCT of the chest; 3) a decrease in FVC between 5–10% with worsening respiratory symptoms (dyspnea and dry cough); or 4) worsening dyspnea with progression of fibrosis on HRCT in the previous 24 months despite treatment. As a definition of progression, some experts also include a decrease in FVC between 5–10% with worsening DLCO >15% [54].

PPF has been described in many CTDs [13,23], but this progressive feature is more frequent in SSc and RA. In SSc-ILD, 67% of patients will present pulmonary progression at 5 years. Of these, 32–33% have PPF [20]. Different variables associated with an increased risk of progression in SSc-ILD have been identified and are summarized in Table 4 [55–57]. Two simple algorithms have also been proposed to stratify the prognosis of these patients (Goh et al. and the SPAR model), which are shown in Figure 1 [58,59].

In RA-ILD, 53% of patients will progress, with an estimated 40% of patients meeting criteria for progressive fibrosing RA-ILD at 5 years of evolution [13,23,60]. The main prognostic factors for pulmonary progression and mortality in RA-ILD are also shown in Table 4 [61]. The usefulness of the gender, age, physiology (GAP) and composite physiological index (CPI) in predicting the risk of mortality in these patients has been demonstrated [21,62,63].

Knowledge of the prognostic factors in these two entities (SSc-ILD and RA-ILD) allows early identification of patients with a potentially higher severity profile who are candidates for intensive targeted treatment as soon as the diagnosis of ILD is established and for close clinical follow-up.

4. Treatment and follow-up

The treatment of CTD-ILD should be individualized and comprehensive and should be planned considering the underlying CTD, the patient's comorbidities, and the severity of extrapulmonary manifestations. In any case, the choice of treatment should always seek a balance between the preservation of pulmonary function and the risk of adverse events.

So far, low-dose glucocorticoids are usually used as initial treatment in monotherapy or in combination with immunosuppressants agents. There are no randomized controlled trials (RCTs) that have evaluated the efficacy of glucocorticoids in CTD-ILD and the evidence supporting their use is based primarily on clinical experience and real-life data. Glucocorticoids should be used with caution in SSc since their use, especially at medium or high doses, is an independent risk factor for the development of scleroderma renal crisis [64]. The efficacy of glucocorticoids in fibrotic patterns (UIP and fibrosing NSIP) is inconclusive. On the contrary, there is accumulating evidence about the detrimental effect of steroids as treatment of PPF [65,66].

Cytotoxic immunosuppressive drugs that are commonly used to treat CTD and CTD-ILD include cyclophosphamide, mycophenolate, azathioprine, calcineurin inhibitors (especially in ILD associated with inflammatory myopathies) and leflunomide (in RA). Despite their use in all CTDs, their efficacy has only been demonstrated in RCTs in the case of cyclophosphamide and mycophenolate for the treatment of SSc-ILD [67,68], with none of them having a therapeutic indication.

Methotrexate has classically been discouraged in patients with RA-ILD because of the risk of causing acute pneumonitis. However, the literature confirms that the actual risk of drug-induced pneumonitis is very low (0.3%) [69–71]. There is no confirmation that methotrexate increases the risk of developing ILD in patients with RA, but recent studies suggest that RA

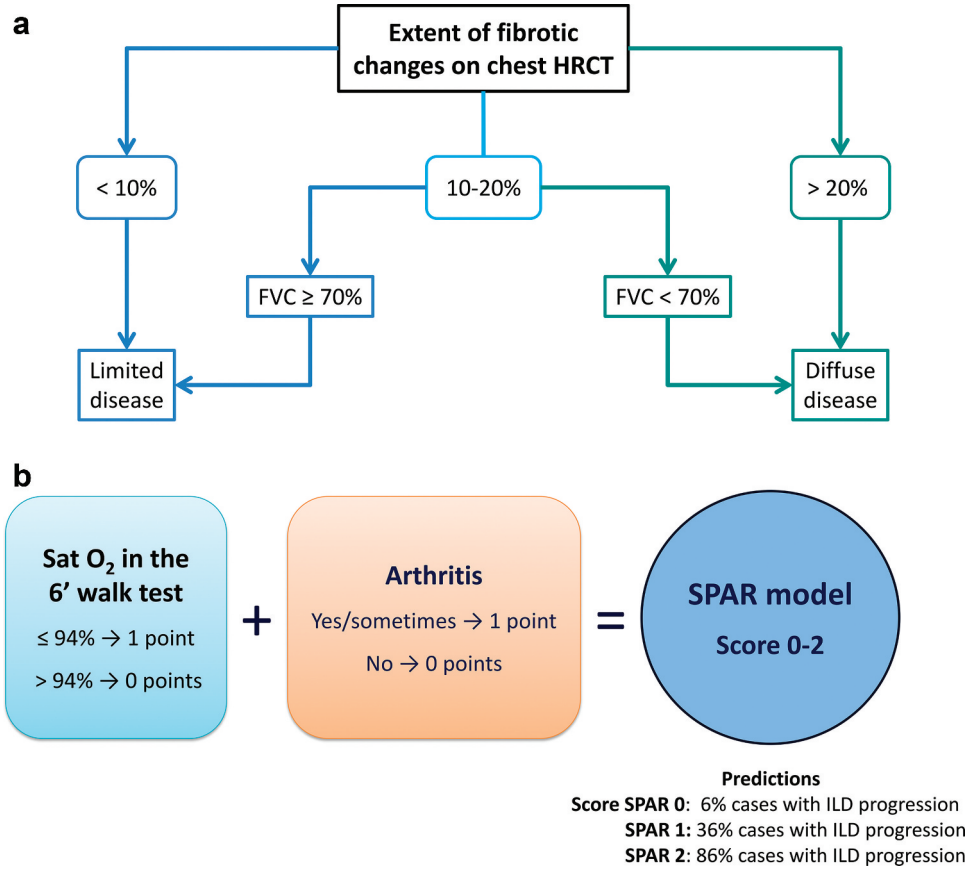

Figure 1. Proposed algorithms to stratify the prognosis of patients with interstitial lung disease associated with systemic sclerosis (SSc-ILD). (a). Algorithm proposed by Goh et al. [58] (b). SPAR model [59] FVC, forced vital capacity; HRCT, high-resolution computed tomography.

control achieved with this drug is associated with a delay in the onset of ILD and a better prognosis [36,72–76].

In case of ILD progression, despite initial treatment with glucocorticoids and immunosuppressants, there are several options: rescue therapy with biologic drugs (rituximab, tocilizumab or abatacept) particularly in ILDs with inflammatory features or patterns. Antifibrotic treatment can be used in CTD-ILD patients with PPF despite previous management . In SSc, the option of autologous hematopoietic stem cell transplantation is also available, although its effect on the lung remains controversial [77–80].

Regarding evidence for the efficacy of biologic agents in the treatment of CTD-ILD, only tocilizumab has confirmed effectiveness in RCTs, specifically in SSc-ILD [81–83]. Although the trials only included patients with mild-to-moderate ILD, tocilizumab has recently been approved by the Food and Drug Administration (FDA) for the treatment of SSc-ILD. There are several ongoing RCTs with rituximab and abatacept (RECITAL and EVER-ILD in SSc-ILD, and APRIL in RA-ILD) [84–86]; currently, however, their use is only supported by real-life observational studies demonstrating their usefulness in stabilizing or improving lung function, particularly in patients with a non-UIP radiological pattern, including cases in which ILD worsened despite previous treatment with glucocorticoids and classic synthetic disease-modifying antirheumatic drugs (DMARDs) or immunosuppressants [87–89].

There are currently two antifibrotic agents on the market: nintedanib and pirfenidone. At present, only nintedanib has been approved by the FDA and the European Medicines Agency (EMA) for the treatment of fibrosing SSc-ILD, based on data from the phase III RCT SENSCIS [90], and for the treatment of other progressive fibrosing ILD, including CTD-ILD, based on results from the phase III RCT INBUILD [53].

Pirfenidone does not have data in CTD-ILD with fibrosis and a progressive phenotype but only in a few disease entities that are under the designation of CTD. The published experience with pirfenidone in CTD-ILD is so far limited to two phase II RCTs (LOTUSS and RELIEF) [91,92]. Ongoing studies include a phase III RCT in SSc-ILD (Scleroderma lung study III) [93] and a phase II in RA-ILD (TRAIL 1) [94].

Equally relevant non-pharmacological measures within the comprehensive approach include smoking cessation, respiratory rehabilitation, prevention and treatment of gastroesophageal reflux, systematic vaccination against respiratory pathogens such as influenza, pneumococcus and SARS-CoV -2, adequate and early treatment of coexisting respiratory infections, psychosocial support, and long-term home oxygen therapy in the presence of chronic respiratory failure.

When PPF does not show stabilization, despite the measures taken, lung transplantation should always be considered in candidate patients and the case should be referred to Lung Transplant Units before reaching an advanced stage of respiratory involvement.

5. Conclusion

CTD-ILD especially those with progressive pulmonary fibrosis have a high morbidity and mortality rate. In order to reverse this situation and improve the prognosis and QoL of patients, a multidisciplinary diagnostic and therapeutic approach is necessary as the best model of care to guarantee early diagnosis and comprehensive and individualized treatment. Antifibrotic drugs are considered for those presenting progressive pulmonary fibrosis.

6. Expert opinion

There are still unmet needs in PPF-CTD, including the need for reliable prognostic biomarkers for early identification and tools to select the most appropriate comprehensive treatment strategy for each patient. It is desirable that, in the coming years, through the identification of biomarkers, genetic polymorphisms and other molecular classification techniques, progress will be made in personalized precision medicine. There are also high expectations for new drugs that could expand the therapeutic arsenal for PPF, such as JAK kinase inhibitors, pentraxin 2, pamrevlumab, and autotaxin inhibitors [95–99].

It is also essential to know the long-term safety and efficacy of combined immunosuppressant and antifibrotic therapy, and to have methods for evaluating the response to treatment that provide a more comprehensive and multifaceted vision, including patient-reported outcomes, because patients should be increasingly empowered in decision-making.

Another area for improvement is the diagnostic delay experienced by these patients, which leads to a delay in treatment initiation. The origin of this delay is usually multifactorial (difficulty of access to an expert multidisciplinary team, waiting lists in the referral circuits, and in the performance of complementary examinations such as HRCT or PFTs, and failure to detect respiratory symptoms or signs early), so its solution seems difficult, since it implies better planning of resources and training programs for clinicians who care for these patients, whether in primary or specialized care.

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