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Connective tissue disease-associated interstitial lung disease

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ABSTRACT

Connective tissue disease-associated interstitial lung disease (CTD-ILD) represents a group of systemic autoimmune disorders characterized by immune-mediated organ dysfunction. Systemic sclerosis, rheumatoid arthritis, idiopathic inflammatory myositis, and Sjögren's syndrome are the most common CTDs that present with pulmonary involvement, as well as with interstitial pneumonia with autoimmune features. The frequency of CTD-ILD varies according to the type of CTD, but the overall incidence is 15%, causing an important impact on morbidity and mortality. The decision of which CTD patient should be investigated for ILD is unclear for many CTDs. Besides that, the clinical spectrum can range from asymptomatic findings on imaging to respiratory failure and death. A significant proportion of patients will present with a more severe and progressive disease, and, for those, immunosuppression with corticosteroids and cytotoxic medications are the mainstay of pharmacological treatment. In this review, we summarized the approach to diagnosis and treatment of CTD-ILD, highlighting recent advances in therapeutics for the various forms of CTD.

Keywords: Lung diseases, interstitial; Collagen diseases; Scleroderma, systemic; Arthritis, rheumatoid; Myositis; Therapeutics.

INTRODUCTION

A group of systemic autoimmune illnesses known as connective tissue diseases (CTDs) are defined by immune-mediated organ failure. All CTDs have a chance of developing to interstitial lung disease (ILD), but some individuals have a higher risk of developing it, such as those who have systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM), Sjögren's syndrome (SS), mixed CTD, and systemic lupus erythematosus (SLE).[1] In some cases, a definitive CTD diagnosis is not possible despite some suggestive clinical and laboratorial findings. This is called interstitial pneumonia with autoimmune features (IPAF). The main hypothesis for the pathogenesis of CTD-ILD is that fibrosis is preceded by an immune-mediated process that has distinct features in SSc, RA, IIM, and SS.[2]

Patients with CTD-ILD with decreased FVC and/or DL_{CO}, and fibrotic signs on HRCT have a worse prognosis than do those with CTD without ILD. Knowledge on ILD influences treatment choices and directs surveillance. However, who should be screened for ILD is not well established for CTDs, with the exception of SSc, in whom HRCT should be done at the moment of diagnosis. Additionally, HRCT can assist to determine the extent and severity of the disease since the presence of bronchiectasis and honeycombing is linked to a higher risk of progression.[3] Another difficult decision is how patients should be monitored, in which cases ILD should be treated, and in whom the therapy should be discontinued.

The management of CTD-ILD is the main topic of this review. Therefore, treatment of comorbid conditions such as pulmonary hypertension, gastroesophageal reflux, airway disease, and bone health will not be addressed.

SSC-ASSOCIATED ILD

SSc is characterized by autoimmunity, vasculopathy, and fibrosis, and may be associated with a high mortality rate.[4] ILD is a common disease feature and, along with pulmonary hypertension, represents the main cause of death. As a result, ILD evaluation is advised as a part of the initial assessment and follow-up of patients with SSc.[5] Every patient should receive an ILD-related physical examination with special attention to the presence of crackles since this is a marker of fibrosis and, consequently, of disease severity. Screening should be done with HRCT, FVC measurement, and, when available, DL_{CO} determination, for all SSc patients at baseline. Nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) are the most common ILD patterns linked to SSc, and their estimated prevalence ranges from 30-40% in clinically relevant cases to up to 80% in asymptomatic presentations. For longitudinal follow-up, in the first 3-5 years after disease diagnosis, pulmonary function tests (PFTs) should be performed every 3-6 months. HRCT should be performed every 12-24 months, depending on the risk of disease progression. High risk factors, such as lower FVC and DL_{CO}, increases in disease extension on

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HRCT, or presence of anti-Scl-70, should prompt more frequent HRCT (every 12 months). New onset of symptoms or changes in PFT results requires close evaluation (Figure 1).[6-8]

The likelihood of disease progression, the degree of extrapulmonary disease, and the patient's risk of developing severe disease should all be taken into account when deciding whether to start treatment.[7] Also, it is important to evaluate risk factors for disease progression, such as African-American ethnicity, older age at disease onset, male sex, short disease duration, and presence of anti-Scl-70 or RNA polymerase III. Therefore, patients with subclinical disease—asymptomatic patient, minimal-to-mild extension of ILD on HRCT, normal pulmonary function—and with low risk factors for ILD could be monitored in a certain way. However, patients with clinical ILD or subclinical ILD who are highly at risk of disease progression should be started on pharmacological therapy.

Treatment of SSc is challenging because of its heterogeneous disease manifestations, and the preference is for therapies that may target more than one active organ system. However, SSc is the CTD-ILD with the most robust scientific evidence. Treatment includes the use of immunosuppressants and antifibrotics (Figure 2).

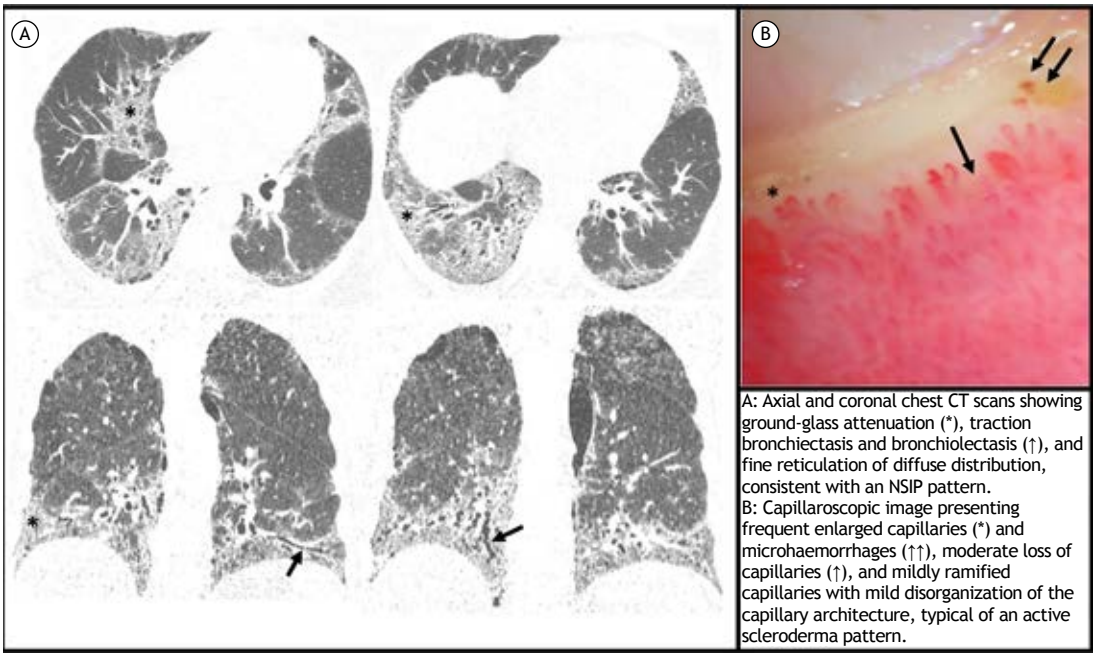
Due to the increased risk of scleroderma-related renal crises, corticosteroids should be prescribed with caution in SSc patients.[9]

Cyclophosphamide modulates regulatory T cells, decreasing the secretion of IFN-γ and IL-12. Tashkin et al.,[10] based on the Scleroderma Lung Study (SLS) I, found that cyclophosphamide was linked to improvements n FVC in % of predicted values (FVC%) after 12 months of oral cyclophosphamide (2 mg/kg per day) over placebo and that the benefit was sustained for 24 months. However, adverse events were more common in the cyclophosphamide group.

Mycophenolate impairs both T-cell proliferation and B-cell proliferation. In the SLS II, the use of mycophenolate for 24 months (1,500 mg twice daily) was compared with 12 months of oral cyclophosphamide (2 mg/kg per day).[11] With regard to efficacy endpoints, there was no discernible difference between treatments; however, mycophenolate showed less toxicity. Hence, mycophenolate emerged as a first-line therapy for SSc-ILD.[12] If mycophenolate cannot be tolerated, intravenous pulses of cyclophosphamide could be used at 750 mg/m^2 monthly.

Tocilizumab is a monoclonal antibody that blocks the IL-6 receptor. Both phase 2 and phase 3 trials of tocilizumab versus placebo for early diffuse cutaneous SSc showed no significant difference in the primary outcome, skin fibrosis.[13,14] The secondary endpoint (changes from baseline FVC%) in the phase 3 trial revealed a significant difference at 48 weeks, favoring tocilizumab.[14] A post-hoc analysis revealed that patients with fibrosis (65%) had FVC% stabilization.[15] Even though there have been no tests comparing tocilizumab with mycophenolate or cyclophosphamide, this finding suggests that tocilizumab may be an option for individuals with early disease-related cutaneous SSc-associated ILD and high C-reactive protein levels.

Rituximab is an anti-CD20 monoclonal antibody that depletes peripheral B cells. A randomized controlled trial (RCT) of rituximab (375 mg/m^2 once weekly) versus placebo for four weeks led to significant improvement in skin fibrosis,[16] but 89% of the patients had ILD, and



A: Axial and coronal chest CT scans showing ground-glass attenuation (*), traction bronchiectasis and bronchiolectasis (↑), and fine reticulation of diffuse distribution, consistent with an NSIP pattern.
B: Capillaroscopic image presenting frequent enlarged capillaries (*) and microhaemorrhages (↑↑), moderate loss of capillaries (↑), and mildly ramified capillaries with mild disorganization of the capillary architecture, typical of an active scleroderma pattern.

Figure 1. HRCT scans (in A) and capillaroscopy features (in B) in a patient with systemic sclerosis. NSIP: nonspecific interstitial pneumonia.

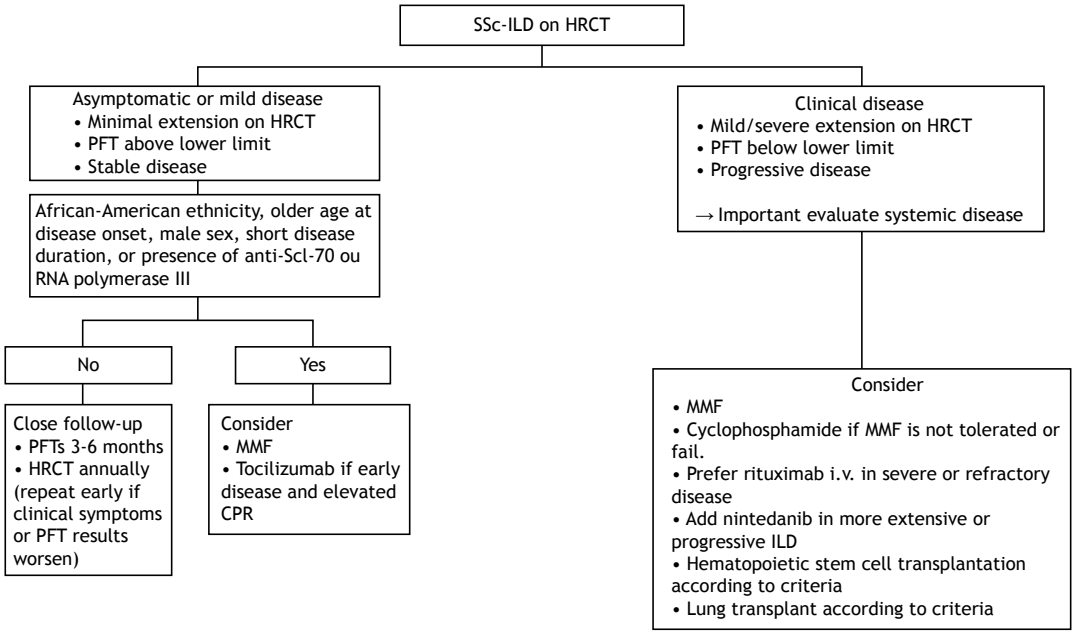


Figure 2. Treatment algorithm for systemic sclerosis-associated interstitial lung disease (SSc-ILD) based on evidence and expert opinion. PFT: pulmonary function test; MMF: mycophenolate; and CPR: C-reactive protein. Modified from Roofeh et al.[7]

there was a favorable effect on changes in FVC% at six months.[17] A phase 2 RCT of rituximab (designated RECITAL) used 1,000 g at day 0 and at day 15 versus a monthly pulse of intravenous cyclophosphamide 600 mg/m^2 in severe or progressive CTD-ILD patients and showed that FVC% improved from baseline in both arms after four months, but rituximab caused fewer adverse events.[18] The study included 38% of patients with SSc.[18] Individuals with refractory multisystemic disease are difficult to treat and rely heavily on expert judgment. If mycophenolate fails, one option is to replace it with cyclophosphamide[19] or rituximab.[20]

Nintedanib is an antifibrotic medication that blocks tyrosine-kinase receptors (PDGF and VEGF receptors). An RCT (SENSCIS) in patients with SSc-ILD compared nintedanib 150 mg twice a day with placebo in patients showing fibrosis affecting at least 10% of the lungs and showed that the nintedanib arm had a slower rate of decline in FVC over 52 weeks.[21] Prior to enrollment, 48% of patients were taking a stable dose of mycophenolate, and patients assigned to receive mycophenolate plus nintedanib had the slowest decline in lung function. However, it is important to notice that patients in that RCT were randomized for nintedanib but not for mycophenolate. Patients who had early SSc, elevated inflammatory markers, or extensive skin fibrosis had a more rapid decline in FVC, and nintedanib had a numerically greater effect on these patients.[22] Nintedanib was also studied in patients with progressive pulmonary fibrosis in the RCT designated INBUILD.[23] Almost a quarter of the patients had CTD-ILD (mostly SSc and RA). Although the study lacked power to show subgroup efficacy, it did show an overall reduction in ILD progression. Nintedanib is not typically used as first-line therapy, because no improvement in lung function has been shown in any study.

Pirfenidone is also an antifibrotic whose precise pharmacodynamics is yet to be known. It has been confirmed that it inhibits TGF-β expression and PDGF production, as well as having an anti-inflammatory effect. A phase 2 trial in patients with SSc-ILD (LOTUSS) evaluated pirfenidone with either 2- or 4-week titration up to 2,403 mg/day for 16 weeks.[24] SLS III is an RCT that compared the combination of mycophenolate plus pirfenidone, mycophenolate alone, and placebo.[25] Recruitment was prematurely stopped due to COVID-19, and only one-third of the calculated sample size was included. There was no difference in adding pirfenidone to the mycophenolate regimen in an 18-month period, and both groups showed improvements in FVC% when compared with placebo, although the combination mycophenolate plus pirfenidone presented with a more rapid improvement over 6 months and showed a trend toward fewer fibrosis areas on HRCT.

According to a recent American Thoracic Society (ATS) guideline,[26] the evidence for treatment of SSc-ILD is strong for mycophenolate and conditional for cyclophosphamide, tocilizumab, rituximab, nintedanib, and mycophenolate plus nintedanib. The recommendation for the use of pirfenidone requires further research, and the use of corticosteroids should be done with caution, with doses of no more than 15 mg/day.

Hematopoietic autologous stem cell transplantation has emerged as a therapy capable of the greatest improvements in ILD and skin disease. However, because of its high potential for life-threatening adverse effects, it is usually a second-line therapy in patients with early diffuse SSc and a first-line approach after failure. Three trials have presented improvements in survival, skin fibrosis, FVC, and quality of life when compared with therapy with cyclophosphamide.[6]

RA-ASSOCIATED ILD

RA is a chronic, inflammatory disease that affects more women than men and peaks in the sixth decade of life. ILD is one of the most common and severe complications of RA, accounting for 10-20% of deaths (the second leading cause).

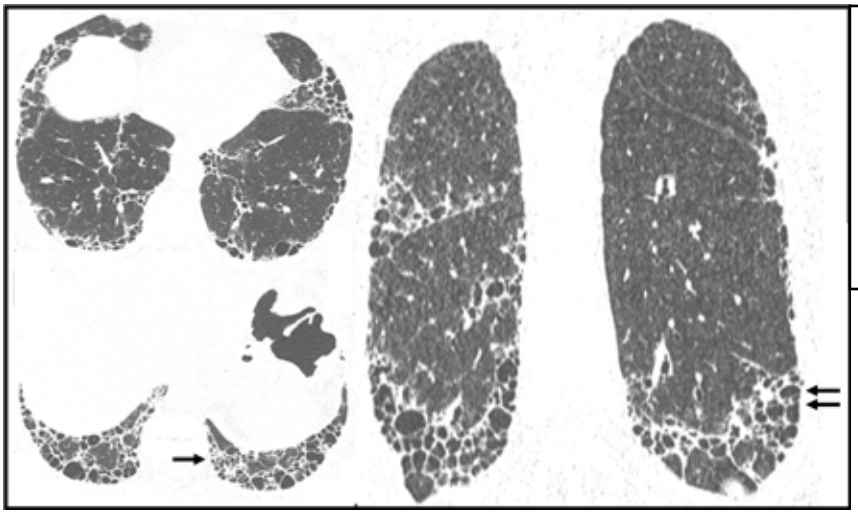
The estimated prevalence of clinically significant RA-ILD is between 10% and 30% and, differently from other CTD-ILD, UIP is the most common pattern (Figure 3).[8,27] Because non-UIP patients respond better to anti-inflammatory and immunosuppressive therapy, identifying the pattern could have therapeutic implications. Recommendations for initial evaluation and follow-up of patients with RA are less clear than are those for SSc, but the possibility of ILD should be considered based on its incidence and prevalence. For initial screening, patients who exhibit symptoms or Velcro crackles on respiratory auscultation should undergo HRCT and PFT (FVC and DL_{CO}). When there are no symptoms and auscultation is unremarkable, the choice for screening should be individualized on the basis of risk variables such male sex, advanced age, late onset of disease, disease duration, history of smoking, elevated rheumatoid factor and/or anticitrullinated protein levels, and disease activity.[27,28] There is some evidence that chest X-ray, spirometry, and pulse oximetry findings could identify pulmonary involvement in respiratory asymptomatic patients with RA.[29]

Disease activity should be monitored with clinical evaluation, PFTs, and six-minute walk tests every 3-6 months and with HRCT every 12-24 months, or if functional deterioration, treatment adjustments, or other respiratory complications are suspected.[6,28] The course of RA-ILD is varied. After diagnosis, some individuals have steady or even improved lung function results, while others experience lung function deterioration that is typically moderate but can occasionally be sudden.[30]

Usually, half of RA-ILD patients will have stable or slowly progressing ILD; therefore, risk factors for progression, such as UIP pattern, increased anticitrullinated protein levels, degree of worsening from baseline of PFT results, and significant fibrotic alterations on HRCT, should be monitored. A few studies, however, have shown that, after controlling for age, smoking, and PFT, UIP pattern is not an independent predictor of mortality.[31]

The treatment of RA-ILD is complex for various reasons. First, there have been few controlled studies on RA-ILD. Second, both conventional and biological disease-modifying antirheumatic drugs (DMARDs) have been linked to pulmonary toxicity. Third, there is no evidence that RA treatment reduces lung involvement, and immunosuppressive drugs commonly used to treat ILD do not always control the articular disease. This means that treating ILD secondary to RA is not the same as treating RA in a patient who also has ILD. Close monitoring is usually required in an asymptomatic patient with nonprogressive ILD (Figure 4).

Methotrexate is an important conventional DMARD (cDMARD) for RA treatment. Pulmonary toxicity of methotrexate is rare and, when present, it is subacute, presents as a hypersensitivity pneumonitis, usually occurring during the first year of treatment, and is dose dependent. However, an increasing body of evidence has revealed that methotrexate is negatively related to the occurrence of RA-ILD and does not appear to raise the risk of ILD.[32] As a result, in individuals with



Axial chest CT showing reticulation, traction bronchiectasis and bronchiolectasis (↑), and honeycombing (↑↑) with basal predominance, consistent with a UIP pattern. Coronal slice showing a straight interface between fibrosis and normal lung - straight-edge sign.

Figure 3. HRCT features in a patient with rheumatoid arthritis. UIP: usual interstitial pneumonia.

ILD, a personalized assessment for methotrexate use is advised.

Corticosteroids alone or in combination with cDMARDs or immunosuppressive drugs are usually used in the treatment of RA-ILD. Nevertheless, a British study discovered that patients with RA-ILD had a greater mortality rate when using long-term corticosteroid therapy due to an increased incidence of infection.[33] It is important to notice that there is lack of evidence from controlled studies, and recommendations are extrapolated from idiopathic pulmonary fibrosis and other CTD-ILD cohorts.

Mycophenolate and cyclophosphamide are also options for first-line treatment of RA-ILD, although there are no large RCTs. Mycophenolate (2,000-3,000 mg/day) was associated with improvement in symptoms and PFT results in CTD-ILD cohorts that included RA-ILD patients.[34] In patients with non-UIP pattern, there was improvement in FVC% and DL_{CO}% and, in cases with a UIP pattern, there was stabilization.[35] Cyclophosphamide is used in clinical practice, especially in cases of rapid progression of ILD, but with limited efficacy data.[36] Mycophenolate is considered the main alternative to cyclophosphamide due to the lower rate of side effects and possible better survival.[37] Because cyclophosphamide and mycophenolate do not normally control articular disease, they are often used with other immunosuppressants.[38]

Treatment options with other DMARDs, such as biologic (bDMARD) or targeted synthetic (tsDMARD) DMARDs require distinguishing between treating RA in a patient who also has ILD and treating a patient with ILD associated with RA. Furthermore, most studies lacked a control group and excluded patients with active ILD. As a result, conclusions about those treatments are largely subjective and based in opinion.

All anti-TNF-α agents have been associated with lung toxicity, with a prevalence of 0.5-3.0%.[39] It usually occurs within the first six months after treatment initiation, is usually severe, and has high mortality rates. Age, pre-existing ILD, and concurrent use of methotrexate or leflunomide are all risk factors for the development of this complication.[38] Experimental investigations suggest that anti-TNF-α could have both profibrotic and antifibrotic actions. Therefore, an imbalance between these two roles may trigger or stabilize ILD.[40] In patients with RA who are using anti-TNF-α and present with stable ILD, there is no conclusive evidence about discontinuation of the drug.

Treatment with tocilizumab (8 mg/kg i.v. every 4 weeks or 162 mg s.c. weekly) in RA-ILD patients has conflicting published data, because it could be associated with the development of ILD, with worsening of pre-existing ILD,[41] and with improvement or stabilization of lung function.[42] Furthermore, there is evidence that the worsening of ILD could be related to RA disease activity more than to drug toxicity.[43]

Abatacept is emerging as a safer alternative for RA-ILD patients who require biological therapy.[44] However, in a retrospective cohort analysis, there was no difference in the risk of ILD-related complications with the use of abatacept, rituximab, or tocilizumab when compared with anti-TNF-α therapy.[45]

Rituximab is also the preferred DMARD to treat RA articular activity when RA-ILD is present because of its articular and pulmonary efficacy,[46] with low incidence of new cases of ILD (0.4%), which is probably associated to disease activity rather than to drug toxicity.[47] Moreover, there is evidence of stabilization of ILD in progressive RA-ILD.[48,49] Some evidence suggests that long-term rituximab treatment raises the risk of respiratory or urinary infections as a result of the development of the side effect of hypogammaglobulinemia.[50]

Patients treated with tofacitinib (a Janus kinase inhibitor), when compared with those treated with adalimumab, had a decreased incidence of ILD, according to a retrospective study with a large cohort of RA patients, a finding that indicates that tofacitinib might have a good safety profile.[30,39]

Antifibrotics such as nintedanib have been shown in an RCT to slow the progression of fibrotic RA-ILD with a progressive phenotype.[23] In that RCT, progressive pulmonary fibrosis (PPF) was defined as meeting at least one of the following four criteria within the last 24 months: a relative decline of at least 10% of FVC%; a relative decline of at least 5% of FVC% plus

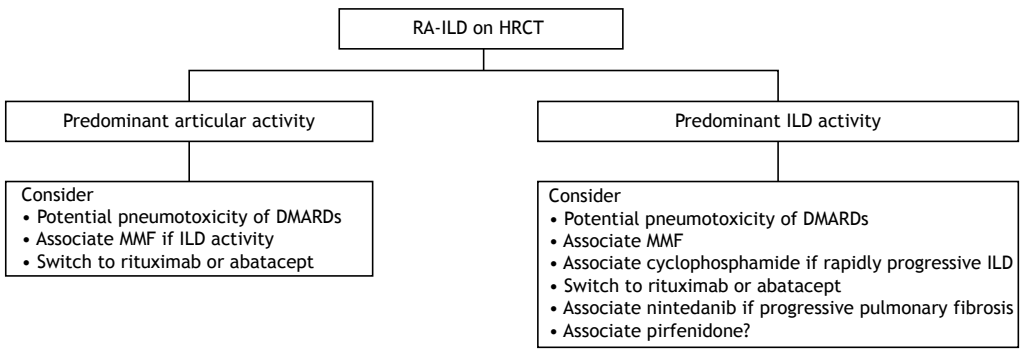


Figure 4. Treatment algorithm for rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on evidence and expert opinion. DMARDs: disease-modifying anti-rheumatic drugs; and MMF: mycophenolate.

worsening of respiratory symptoms; increase in fibrosis on HRCT; or worsening of respiratory symptoms and increase in fibrosis on HRCT. Regarding pirfenidone, a phase 2 RCT comparing the effectiveness of oral pirfenidone (2,403 mg/day) with that of placebo in patients with RA-ILD was terminated early due to slow recruitment secondary to COVID-19.[51] Although the primary endpoint was not met, results suggest that the pirfenidone group had a slower rate of decline of FVC. A single-center prospective controlled cohort study involving CTD-ILD patients (RA-ILD patients, 17%) compared the use of pirfenidone with a control group and found improvement in DL_{CO} in the pirfenidone RA-ILD group.[52] Recently, an official ATS/European Respiratory Society (ERS)/Japanese Respiratory Society/*Asociación Latinoamericana de Tórax* clinical practice guideline[53] has defined the concept of PPF with some differences when compared with a previous RCT on the topic.[23] The committee has suggested the use of nintedanib for the treatment of PPF, but not of pirfenidone, suggesting further research regarding that drug.

Important nonpharmacological interventions include smoking cessation, respiratory rehabilitation, immunization, and long-term oxygen therapy when indicated.

IIM

Immune-mediated muscle injury characterizes a group of illnesses known as idiopathic inflammatory myositis. There are many illnesses that afflict adults, such as dermatomyositis, polymyositis, and antisynthetase syndrome (AS). The pathogenesis and clinical presentation of each condition varies, particularly in terms of the presence or absence of extramuscular symptoms, such as skin and lung involvement.

New classification criteria were validated in 2017 by the European League Against Rheumatism and the American College of Rheumatology (ACR).[54] These criteria classified patients as having "definite", "probable", or "possible" disease. The presence of autoantibodies could be identified in over 50% of patients, and they can be divided in myositis-associated autoantibodies—anti-Ro52, anti-RNP, anti-Ku, anti-Pm Scl—and myositis-specific autoantibodies—anti-tRNA, anti-MDA5, anti-Mi2, anti-SRP, anti-TIF1g, and anti-NXP2. Also, antibodies bound to the cytoplasm are frequently seen with screening for antinuclear antibodies. AS is characterized by mechanic's hands, Raynaud's phenomenon, and the presence of anti-aminoacyl tRNA synthetase (ARS) antibodies. These cases are usually amyopathic.

With prevalence between 17% and 36%, ILD is the most common extrapulmonary involvement in IIM and the main cause of death. Patients with AS have an increased risk of ILD, and it may precede muscle symptoms in up to 20% of cases.[55] The exact distribution of radiological patterns of ILD stratified by different myositis-specific autoantibodies remains unclear, but HRCT can present with an organizing pneumonia pattern, an NSIP pattern, or an overlap of these two, especially in patients with ARS and anti-MDA5 antibodies (Figure 5). The UIP pattern is less common and may have a better prognosis than in idiopathic pulmonary fibrosis patients. CTD-associated UIP is more closely associated with signs such as the straight-edge sign, exuberant honeycombing, and anterior upper lobe sign.[56] Fibrotic ILD is associated with a worse prognostic.

There are no established guidelines for the treatment of IIM-ILD; instead, treatments vary widely and are frequently based on case studies or retrospective evaluations. An important differentiation should be made between chronic ILD, in which low-dose corticosteroids associated or not with immunosuppressive therapy will be needed, and rapidly progressive ILD, which often requires a more aggressive combination of immunosuppressive drugs (Figure 6).

Corticosteroids are the mainstay of IIM-ILD therapy and are typically used as a first-line strategy. Stable patients should receive 0.5-1.0 mg/kg per day of prednisone or its equivalent for 4 to 8 weeks, followed by gradual tapering over months.[57] Muscle enzyme levels may serve as guidance for tapering (when initially increased). A meta-analysis showed improvement rates with the use of corticosteroids alone in 89% of cases.[57] For rapidly progressive and severe disease, pulses of 1,000 mg of methylprednisolone could be used for 3 days. Data suggest that, in such cases, corticosteroids alone should have response rates of 50% and immunosuppressive therapy should be combined in advance.[55,57] Additional immunosuppressive drugs (steroid-sparing agents) could be used in patients who do not respond to or tolerate corticosteroid tapering.

Calcineurin inhibitors (cyclosporine A and tacrolimus) act by inhibiting IL-2-mediated CD4 T cell activation. Cyclosporine can be used in a dose of 4 mg/kg per day, maintaining plasma levels between 300 and 350 ng/mL, with improvement rates of 75%.[57] Tacrolimus is also an option.[58]

Azathioprine is a purine analogue that also blocks T-cell and B-cell proliferation. There are relatively few retrospective studies reporting safety in about two-thirds of ILD cases, with typical dosages of 2-3 mg/kg per day, showing good safety profile.[55] However, it is difficult to evaluate response, because many studies had different IIM diagnoses (which overlapped IIM/SSc and AS) and rarely described criteria response.[59]

Mycophenolate at a dose of 2,000-3,000 mg/kg per day is commonly used to treat IIM-ILD, and several studies have shown that it can stabilize or improve PFT results while reducing daily steroid doses.[33,60] One study suggests an efficacy of approximately 80% in treating IIM-ILD with a good safety profile.[55]

The use of cyclophosphamide is usually limited to most aggressive forms of IIM-ILD, favoring i.v. administration, and has been shown to improve both muscle strength and FVC and DL_{CO}.[61] It has also

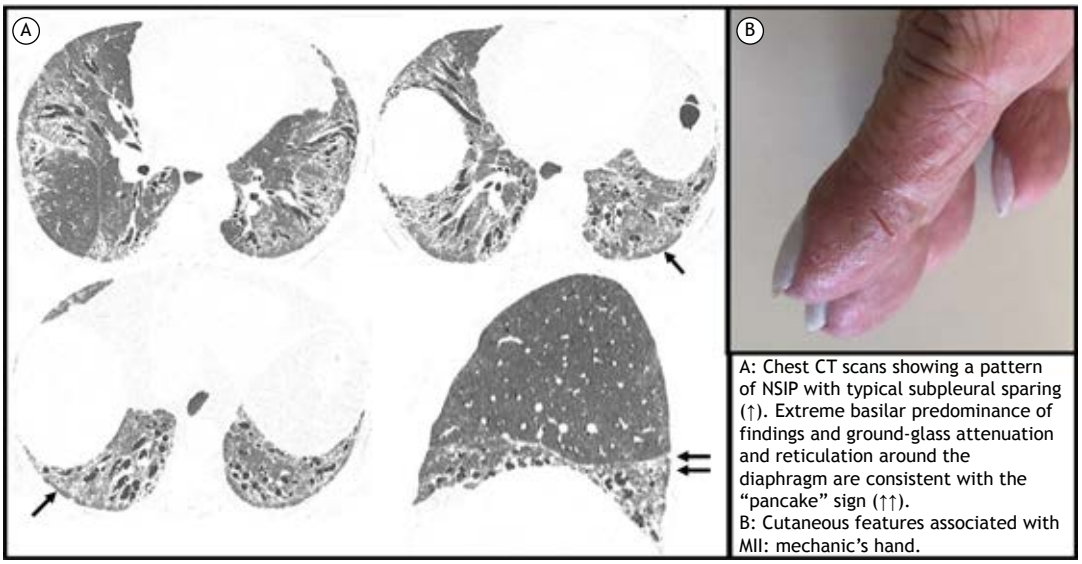


Figure 5. HRCT scans (in A) and cutaneous features (in B) in idiopathic inflammatory myopathy (IIM). NSIP: nonspecific interstitial pneumonia.

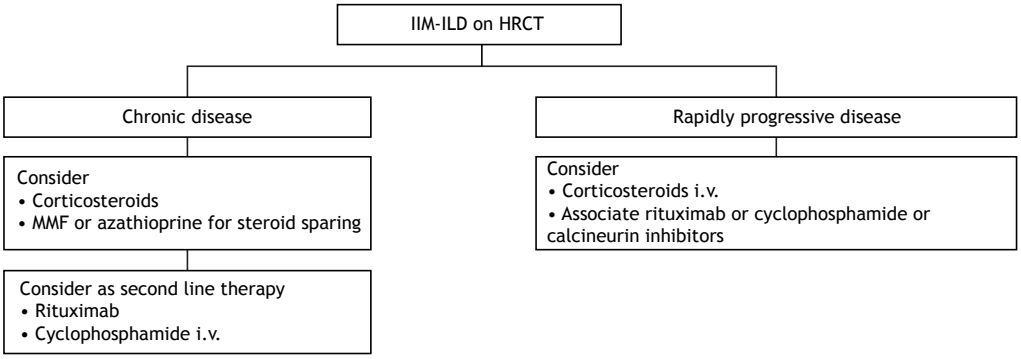


Figure 6. Treatment algorithm for idiopathic inflammatory myositis-associated interstitial lung disease (IIM-ILD) based on evidence and expert opinion. MMF: mycophenolate. Modified from Barba et al.[57] and Morisset et al.[59]

been used with cyclosporine A and a corticosteroid in cases of rapidly progressive disease or when initial management fails. A phase 2 RCT comparing the use of cyclophosphamide and that of rituximab in CTD-ILD patients, 45% of whom had IIM, showed that both arms had increases in FVC with no superiority of rituximab.[18] However, the rituximab arm experienced fewer adverse events.

Rituximab 1,000 mg at day 0 and day 15 has been shown to improve IIM-ILD in several retrospective studies.[62-64] Patients with IIM-ILD (particularly AS) appear to respond better than do patients with other CTD-ILD.[65] Rituximab is also the drug of choice in cases of refractory IIM-ILD. Intravenous immunoglobulin (more commonly used for active muscle disease) and tofacitinib (a Janus kinase inhibitor) are also described as potential treatments.[66]

OTHER CTDS

Here we remark some treatment information for CTD-ILD with more scarce data. Besides that, patients with SLE appear to have ILD less frequently and less severe disease when compared with patients with other CTDs. Therefore, we will not address SLE.

SS

The second most prevalent multisystemic disease after RA is SS. It is more common in women and is characterized by lymphocytic inflammation of exocrine glands, which causes dry eyes and mouth. A large proportion of asymptomatic patients will have abnormal pulmonary imaging, and 10% to 20% of patients will show significant pulmonary involvement.[67]

Prevalence seems to increase over time. Therefore, the ACR published a consensus guideline for SS in 2021.[68] A baseline chest X-ray is recommended for asymptomatic patients, and baseline PFTs are being considered. For symptomatic patients, they recommend HRCT and a complete PFT.[68] Bronchiolitis and bronchiectasis are the most common pulmonary manifestations, but, when present, ILD will manifest as NSIP, UIP, and/or lymphocytic interstitial pneumonia.

SS patients have an increased risk of lymphoma and amyloidosis.[69] Except for ILD with a UIP pattern,[68] a large proportion of the ILDs in SS-ILD patients tend to follow an indolent course.[68]

Corticosteroids are usually prescribed (0.5-1.0 mg/kg per day) and are frequently combined with immunosuppressive drugs such as mycophenolate and azathioprine.[70,71] The ACR guideline recommends second-line therapy with rituximab, cyclosporine, or tacrolimus in cases of moderate to severe ILD in patients who have failed or not tolerated mycophenolate.[68] Nintedanib, either alone or in combination with immunomodulatory agents, should be considered as second-line therapy when fibrotic ILD develops into PPF.[23] Patients with rapidly progressive disease should use intravenous corticosteroids with or without the addition of cyclophosphamide or rituximab.[18,55]

IPAF

Many ILD patients have clinical and/or laboratory characteristics that suggest background autoimmunity, but they lack a CTD that can be distinguished. To classify these patients, the ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD advocated using the name "IPAF," which is a combination of three domains.[72] A clinical domain consisting of extrathoracic characteristics; a serological domain of specific antibodies; and a morphological domain consisting of specific HRCT patterns, histological features, and multicompartment features. Those criteria were reviewed recently, offering insights for future directions with these patients.[73]

The most prevalent findings in IPAF populations evaluated by several centers around the world included female sex, Raynaud's phenomenon, positivity for antinuclear antibodies, and NSIP.[74] Predictors of mortality were age and DL_{CO}. When the HRCT pattern was analyzed, the presence of honeycombing predicted worse survival.[75] Additionally, a meta-analysis revealed that autoantibodies that are highly specific for particular CTDs (serological domains) are less significant in the prognosis of IPAF when compared with radiological-pathological patterns.[76]

There are still many questions regarding IPAF treatment. According to most studies, individuals with non-UIP IPAF have a survival rate comparable to that of individuals with CTD-ILD, and most ILD experts would likely treat them similarly. However, a proportion of IPAF patients demonstrated long-term stability with no treatment. Therefore, IPAF patients may be followed up without medication therapy or be treated with immunomodulation with glucocorticoids and/or immunosuppressants including mycophenolate, azathioprine, cyclophosphamide, calcineurin inhibitors (cyclosporine and tacrolimus), and occasionally rituximab. However, UIP IPAF would result in a more circumspect use of immunosuppression and early evaluation of antifibrotic treatment, particularly when PPF is defined.[77]

Patients who fulfilled IPAF criteria were included in a phase 2 trial of pirfenidone at 2,403 mg/day versus placebo for unclassifiable ILD.[78] There were 12% of patients with IPAF in the pirfenidone arm versus 14% in the placebo arm, and in 5% of both groups, Mycophenolate was used concomitantly. Although results for key secondary endpoints support that pirfenidone treatment slows disease progression, that study[78] has some limitations, because there were some methodological issues in the primary endpoint and in the secondary outcome; IPAF patients presented no statistical difference in FVC change. Regarding nintedanib, a total of 114 patients (17%) in an RCT[23] had unclassifiable ILD; it is unclear how many of them fulfilled IPAF criteria.

Treatment decisions currently need to be made in a multidisciplinary context and based on a thorough assessment of the benefit to determine the risk ratio for each individual patient.

Mixed CTD

Mixed CTD describes a group of systemic autoimmune diseases that share characteristics with one or more than one systemic autoimmune disease. These diseases include RA, SSc, IIM, and SLE. Antibodies against the nuclear ribonucleoprotein autoantigen are thought to be the serological signature of the condition. Pulmonary involvement is a prominent characteristic of mixed CTD; however, most mixed CTD patients remain asymptomatic.

Treatment for ILD-mixed CTD-associated ILD is usually administered based on the predominant overlapping disease feature that presents with stronger evidence. Corticosteroids, mycophenolate, azathioprine, and rituximab are possible options for these patients.[2,79]

ADDITIONAL MANAGEMENT STRATEGIES IN CTD-ILD

A multidisciplinary strategy should be used in the treatment of patients with CTD-ILD. It is crucial to provide assistance with smoking cessation and lung rehabilitation, because these measures could enhance quality of life. Although not formally studied in CTD-ILD, cardiopulmonary rehabilitation is useful for both the ILD component and possible extrathoracic components. The use of oxygen supplementation should be evaluated to ensure that hypoxia is not present at rest, during exercise, or while sleeping.

Vaccination for influenza, pneumococci, COVID-19, pertussis, and herpes zoster should be offered. Also, *Pneumocystis jirovecii* pneumonia prophylaxis should be considered, especially if > 20 mg/day of prednisone or its equivalent are used or if a lower dose is associated with an immunosuppressive drug. Evaluation for latent tuberculosis and other infectious disease (hepatitis B and C, HIV) is advised.[80] Lung transplantation and evaluation for palliative care

should be considered when diseases progress despite treatment (Figure 7).

Additional therapies
Smoking cessation
Pulmonary rehabilitation
Vaccination
Pneumocystis jirovecii prophylaxis
Evaluation for oxygen supplementation
Evaluation for latent tuberculosis and other infectious diseases
Evaluation for lung transplant
Evaluation for palliative care

Figure 7. Suggested additional therapies for treatment of connective tissue disease-associated interstitial lung disease.

FINAL CONSIDERATIONS

ILD influences CTD patients' mortality and morbidity. Therefore, effective management is essential for improving survival. The screening and treatment of patients with CTD-ILD are not supported by strong data, with the exception of SSc-ILD. Immunosuppressants are typically the main treatment for CTD-ILD, although there is a lack of data to support the effectiveness or safety of all currently prescribed drugs.

AUTHOR CONTRIBUTIONS

KMS: substantial contributions to study conception/design, and data acquisition, analysis, and interpretation. CSM and MCAP: data acquisition, analysis, and interpretation. KMS and CACP: drafting of the manuscript and critical revision of the manuscript for important intellectual content. All of the authors agreed to be accountable for all aspects of the study, ensuring that questions related to the accuracy and integrity of any part of the study have been appropriately investigated and resolved. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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