

## Interstitial lung disease in rheumatoid arthritis: Current concepts in pathogenesis, diagnosis and therapeutics

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articular complication and causes symptoms that lead to a deterioration in the quality of life, high utilization of health resources, and an increased risk of earlier mortality. Early in the course of RA-ILD, symptoms are highly variable, making the diagnosis difficult. Therefore, a rational diagnostic strategy that combines an adequate clinical assessment with the appropriate use of clinical tests, including pulmonary function tests and high-resolution computed tomography, should be used. In special cases, lung biopsy or bronchioalveolar lavage should be performed to achieve an early diagnosis. Several distinct histopathological subtypes of RA-ILD are currently recognized. These subtypes also have different clinical presentations, which vary in therapeutic response and prognosis. This article reviews current evidence about the epidemiology of RA-ILD and discusses the varying prevalence rates observed in different studies. Additionally, aspects of RA-ILD pathogenesis, including the role of cytokines and other molecules such as autoantibodies, as well as the evidence linking several drugs used to treat RA with lung damage will be discussed. Some aspects of the clinical characteristics of RA-ILD are noted, and diagnostic strategies are reviewed. Finally, this article analyzes current treatments for RA-ILD, including immunosuppressive therapies and biologic agents, as well as other therapeutic modalities. The prognosis of this severe complication of RA is discussed. Additionally, this paper examines updated evidence from studies identifying an association between drugs used for the treatment of RA and the development of ILD.

**Key words:** Rheumatoid arthritis; Interstitial lung disease; Pathogenesis; Diagnosis; Therapeutic

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### Abstract

Rheumatoid arthritis (RA) is the most common chronic autoimmune inflammatory joint disease. RA-associated interstitial lung disease (RA-ILD) is a major extra-

**Core tip:** This review analyzes current evidence regarding the epidemiology, pathogenesis, diagnosis and treatment of interstitial lung disease associated with

rheumatoid arthritis (RA-ILD). Data regarding differences in the prevalence of RA-ILD in different populations are presented. Updates regarding the pathogenesis of RA-ILD, including genetics, environmental factors, cytokines and autoantibodies, are presented. The paper also reviews the different tests used to diagnose RA-ILD, describes RA-ILD treatment, and discusses studies that were designed to identify a therapeutic response to immunosuppressive drugs or biological agents.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that involves synovial joints and extra-articular organs. Worldwide, the prevalence of RA has small variations. In Mexico, Peláez-Ballestas *et al*<sup>[1]</sup> reported a prevalence of RA of 1.6% (95%CI: 1.4-1.8). Extra-articular manifestations in RA (ExRA) are a frequent complication, affecting approximately 40% of patients with RA<sup>[2]</sup>. Pulmonary involvement is an important ExRA manifestation, as it is associated with a decrease in survival rates<sup>[3]</sup>. Pulmonary involvement can present in a number of ways, such as pleural disease, pulmonary nodules, Caplan's syndrome, bronchiectasis, bronchiolitis, and airway or interstitial disease<sup>[4]</sup>. Of these presentations, interstitial lung disease (ILD) is the most relevant pulmonary complication in terms of morbidity, impairment in quality of life (QoL), and mortality. ILD heterogeneously affects the lung parenchyma; its clinical spectrum ranges from an incidental subclinical finding of diffuse inflammation to a rapidly progressive, life-threatening, end-stage pulmonary fibrosis (PF). Therefore, ILD is a complex extra-articular complication that is classified according to specific clinical, serological, radiological, and histopathological features<sup>[5]</sup>.

## EPIDEMIOLOGY

The prevalence of ILD in RA varies widely and is affected by factors such as country, race, clinical setting, study design, and intensity of assessment. In their study, Bongartz *et al*<sup>[6]</sup> reported a lifetime risk for the development of ILD of 7.7%. Detection of RA-associated ILD (RA-ILD) in the disease's early stages can be difficult and requires a high level of diagnostic suspicion, as well as a systematic strategy for patient evaluation. One diagnostic problem is that in its early stages, RA-ILD can be asymptomatic or have non-specific symptoms, rendering suspicion of this entity

**Table 1** Prevalence of rheumatoid arthritis-interstitial lung disease

Ref.	Number of patients	Study type	ILD (%)
Perez-Dorame <i>et al</i> <sup>[111]</sup>	34	Cross-sectional	34
Giles <i>et al</i> <sup>[154]</sup>	177	Cross-sectional	33
Yin <i>et al</i> <sup>[29]</sup>	71	Retrospective	24.9
Chen <i>et al</i> <sup>[10]</sup>	103	Cross-sectional	61
Solomon <i>et al</i> <sup>[155]</sup>	48	Retrospective	31
Richman <i>et al</i> <sup>[156]</sup>	274	Cross-sectional	3.6
Zou <i>et al</i> <sup>[157]</sup>	110	Cross-sectional	42.7
Mohd <i>et al</i> <sup>[158]</sup>	63	Cross-sectional	44
Al-Ghamdi <i>et al</i> <sup>[159]</sup>	74	Retrospective	10
Teh <i>et al</i> <sup>[160]</sup>	154	Cross-sectional	6.5
Bharadwaj <i>et al</i> <sup>[161]</sup>	140	Cross-sectional	9.29
Zrour <i>et al</i> <sup>[162]</sup>	75	Cross-sectional	49.3

ILD: Interstitial lung disease.

unlikely. Therefore, in these patients, a high level of diagnostic suspicion and a systematic assessment for this complication are mandatory, especially in patients with risk factors for RA-ILD. Some authors have reported that plain X-rays identified RA-ILD in < 5%<sup>[7]</sup> of patients, whereas our group reported a prevalence at routine rheumatology consultation of only 2.7%<sup>[8]</sup>. This prevalence has increased by 20%-30% with systematic evaluation using high-resolution computed tomography (HRCT)<sup>[9]</sup>. On the other hand, when a combination of tests is employed, an increase is observed in the frequency of RA-ILD diagnosis. Chen *et al*<sup>[10]</sup> described a 61% increase in the diagnosis of ILD using a combination of HRCT and pulmonary function tests (PFT). Table 1 illustrates the variability in the prevalence of RA-ILD, according to recent studies.

Although ILD prevalence has been evaluated in a series of studies, only a few studies have identified the incidence of ILD in patients with RA. Cumulative incidence rates for ILD in RA have been observed to be 3.5% over 10 years of follow-up, increasing to 6.3% at 20 years and to 7.7% at 30 years. After adjusting for the risk of death, the lifetime risk of developing RA-ILD is approximately 10%. In a population-based study, the risk of developing ILD among patients with RA is significantly higher than in patients without RA (HR = 8.96); an elevated risk of ILD in RA patients remained after adjusting for age, gender, and smoking<sup>[6]</sup>. Koduri *et al*<sup>[11]</sup>, in a cohort study, reported that the annual incidence rate for the development of RA-ILD was 4.1/1000 person-years (95%CI: 3.0-5.4), with a cumulative ILD incidence at 15 years of 62.9/1000 individuals (95%CI: 43.0-91.7).

## PATHOGENESIS

RA-ILD is considered a multifactorial complication, attributable to a number of factors. Several hypotheses have been formulated to explain its development. To date, the factors most consistently involved in the development of RA-ILD are shown in Table 2 and those

**Table 2 Risk factors for interstitial lung disease in rheumatoid arthritis**

Factors	
Environmental	Cigarette smoking Occupational exposure (silica)
Demographic	Male sex Age ( $\geq 65$ yr)
Genetic	HLA-DRB1 alleles
Clinical	RA duration Anti-CCP (high titers) RF (high titers)
Medications	Methotrexate Leflunomide Sulfasalazine TNF- $\alpha$ inhibitors

RF: Rheumatoid factor; HLA-DRB1: Human leukocyte antigen-DRB-1; Anti-CCP: Anti-cyclic citrullinated peptide; Anti-TNF: Anti-tumor necrosis factor; RA: Rheumatoid arthritis.

can be classified as follows: (1) environmental; (2) genetic; (3) autoimmune (cytokines, autoantibodies); and (4) drug-related<sup>[12]</sup>.

### Environmental factors

Epidemiological factors associated with ILD in RA include aging, smoking, and RA duration. Mori *et al.*<sup>[12]</sup>, in a prospective cohort study, observed a 4.58-fold increase in the risk for development of ILD in patients aged  $\geq 65$  years ( $P = 0.003$ ); additionally, the risk of ILD was higher in males than in females (50% vs 23.2%, respectively; OR = 3.31,  $P = 0.004$ ). A relationship between smoking and an increase in the prevalence of ILD has been identified in several studies. Miyake *et al.*<sup>[13]</sup> observed, in a case-control study, that smoking increases the risk for ILD 2.21-fold. Saag *et al.*<sup>[14]</sup> found a relationship between smoking and ILD, reporting an approximately 3.8-fold increase in the risk for ILD among patients with a smoking history of  $\geq 25$  pack-years. Baumgartner *et al.*<sup>[15]</sup> reported, in a case-control study, that patients with a history of ever smoking or former smoking have 1.6- and 1.9-fold increases in the risk of ILD, respectively. Occupational exposure, such as silica inhalation, contributes to the development of chronic lung inflammation-related ILD<sup>[16]</sup>.

### Genetic factors

Coultas *et al.*<sup>[17]</sup> reported that the prevalence of ILD is approximately 20% higher in males than in females. Aubart *et al.*<sup>[18]</sup> observed that male gender increases the risk for ILD in RA by 3.29-fold ( $P = 0.0013$ ).

Several alleles are associated with an increased susceptibility for RA-ILD; susceptibility to RA-ILD can be triggered by environmental factors, leading to the development of ILD. Mori *et al.*<sup>[12]</sup>, in a prospective cohort study, observed that patients with RA who were carriers of the HLA-DRB1\*1501 and \*1502 alleles had an increased risk for ILD. Michalski *et al.*<sup>[19]</sup> observed that  $\alpha_1$ -antitrypsin-variant phenotypes, particularly non-M<sub>1</sub>M<sub>1</sub>  $\alpha_1$ -antitrypsin, are significantly associated

with PF in patients with RA.

Charles *et al.*<sup>[20]</sup> found an association between antigen HLA-B40 and pulmonary involvement of RA. The authors observed an enhanced risk of approximately 40.54-fold in pulmonary involvement, compared with other ExRA manifestations. Sugiyama *et al.*<sup>[21]</sup> reported an increase in the frequency of HLA-B54 (63.2%) and HLA-DR4 (60%) polymorphisms in patients with ILD-RA compared with controls (11.4% and 37.9%, respectively).

### Cytokines and autoantibodies related to ILD in RA

Several cytokines have been linked to ILD. Chaudhary *et al.*<sup>[22]</sup> observed, in an experimental model of PF, the pro-fibrotic effects of platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF)- $\beta$ . The authors observed that targeting these molecules leads to an attenuation of lung fibrosis, suggesting that these cytokines may constitute a possible target for novel therapeutic approaches. Gochuico *et al.*<sup>[23]</sup> quantified concentrations of TGF- $\beta_1$ , TGF- $\beta_2$ , PDGF-AA, PDGF-AB, PDGF-BB, and interferon gamma (IFN)- $\gamma$  in fluids obtained by bronchoalveolar lavage (BAL) from 3 different group of patients: (1) RA without lung involvement; (2) RA with pulmonary fibrosis (RAPF); and (3) RA with preclinical ILD (RA preclinical-ILD). They observed significantly higher concentrations of PDGF-AB and PDGF-BB in patients with RA-ILD compared with RA patients without PF, suggesting a pro-fibrotic effect of the alveolar microenvironment in RA preclinical-ILD. Interestingly, when the RA-ILD group was sub-categorized into RA with progressive preclinical ILD and RA with stable preclinical ILD, the authors observed significantly higher concentrations of TGF- $\beta_1$  and IFN- $\gamma$  in patients with RA with progressive preclinical ILD vs patients with RA with stable lung disease ( $P = 0.038$  and  $P = 0.044$ , respectively). TGF- $\beta$  is one of the strongest profibrotic cytokines; it triggers lung fibrosis, interacting with connective tissue growth factor (CTGF) to increase the fibrotic process. Ponticos *et al.*<sup>[24]</sup> demonstrated, in an experimental model, that CTGF exerts a direct profibrotic effect on the development of PF through transcriptional activation of collagen gene type 1  $\alpha_2$  (Col1 $\alpha_2$ ). Pro-inflammatory cells, such as macrophages and mononuclear cells, also contribute to the activation of fibrosis by means of interleukin (IL)-4 and IL-13, inducing TGF- $\beta$  production. Jakubzick *et al.*<sup>[25]</sup> observed, in an experimental model of PF, that IL-4 and IL-13 expression was increased in macrophages and mononuclear cells in regions of active fibrosis. Monocyte chemotactic protein (MCP)-1 is also a profibrotic cytokine that exerts its action through chemokine receptor type 2 (CCR2). Moore *et al.*<sup>[26]</sup> observed increased levels of MCP-1 in the CCR2<sup>-/-</sup> model compared with the wild-type ( $P = 0.004$ ) after induction of PF in the wild-type and the CCR2<sup>-/-</sup> experimental models. Furthermore, the authors reported that a lack of CCR2 is a protective

factor against PF. Wilson *et al.*<sup>[27]</sup> described enhanced levels of IL-17 and IL-1 $\beta$  in the BALF of patients with PF, suggesting that these cytokines play a profibrotic role in the lung fibrosis pathway. On the other hand, IL-10, a well-recognized anti-inflammatory cytokine with immunosuppressive effects, has also been related to the induction of PF. Sun *et al.*<sup>[28]</sup> observed, in an experimental model, that overexpression of IL-10 in lung tissue promoted collagen production and induced recruitment of fibrocytes into the lung, leading to the development of PF in mice.

Antibodies to cyclic citrullinated peptides (anti-CCP) and rheumatoid factor (RF) have also been associated with ILD. Yin *et al.*<sup>[29]</sup>, in a retrospective study, observed that serum levels of anti-CCP2 and RF were significantly enhanced in RA-ILD patients compared with RA patients ( $P < 0.001$  and  $P = 0.02$ , respectively). Kelly *et al.*<sup>[30]</sup> identified positive titers for anti-CCP and RF in 94% and 89%, respectively, of RA-ILD patients compared with RA patients (55%,  $P = 0.006$ ; 58%,  $P = 0.01$ ). Furthermore, they reported that anti-CCP and RF act as predictors of ILD in patients with RA ( $P < 0.003$  and  $P < 0.008$ , respectively). Citrullinated proteins are not only restricted to synovial tissue; they have also been detected at extra-articular sites in patients with RA. Bongartz *et al.*<sup>[31]</sup> observed that citrullination occurs inside mononuclear cells in lung tissue in open-lung biopsy specimens from patients with RA-associated interstitial pneumonia. The authors also reported that despite the high specificity of anti-CCP for RA, citrullination was also found in lung tissue from patients with idiopathic interstitial pneumonia. It remains unclear whether distinct citrullinated RA-specific proteins play a key role in the pathophysiological process in RA-ILD.

### Pharmacological agents as risk factors for RA-ILD:

Presently, there is controversy regarding the actual effects of some medications on the development of ILD in patients with RA. Drug-induced ILD can develop within days of treatment initiation or many years after treatment. The major drugs that have been strongly associated with the induction of ILD are methotrexate (MTX), leflunomide (LFN), sulfasalazine (SFZ), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors, such as etanercept, infliximab, and adalimumab. However, other drugs, including d-penicillamine and gold compounds, are also associated with lung damage. There have been recent case reports of the induction or exacerbation of ILD by the newer anti-TNF agents, as well as other biologic agents that act by different mechanisms. This part of the review attempts to highlight the evidence linking these drugs to lung damage, primarily ILD.

### Methotrexate and ILD

MTX is considered by the European League Against Rheumatism to be part of the first-line treatment of RA<sup>[32]</sup>, and several studies have reported an

association between MTX and the development of RA-ILD. Conway *et al.* reported, in a meta-analysis of randomized controlled trials from 1990-2013 that included 22 studies, that MTX treatment is a risk factor for the development of pneumonitis (RR = 7.81; 95%CI: 1.76-34.72)<sup>[33]</sup>. Bongartz *et al.*<sup>[6]</sup> also reported that treatment with MTX confers a 2.3-fold risk for ILD development. However, Sathi *et al.*<sup>[34]</sup> reported, in a prospective study of 223 patients, that the incidence of MTX-induced pneumonitis after 2 years of follow-up was only ~1%, suggesting that pneumonitis is an uncommon complication. Assessing the actual incidence of MTX-induced ILD is difficult because ILD can be observed in patients with RA independently of MTX treatment; furthermore, MTX is frequently used with other drugs that can also be associated with ILD. Therefore, the most useful data regarding MTX-induced ILD come from studies that evaluated this drug as monotherapy. In a systematic review, Salliot *et al.*<sup>[35]</sup> examined the long-term safety of MTX as monotherapy in 21 prospective studies and reported that only 15 of 3463 patients developed pneumonitis, yielding a frequency of 0.43%. Criteria have been proposed for the diagnosis of MTX-induced pneumonitis. In 1987, Searles *et al.*<sup>[36]</sup> proposed the following 9 criteria for the diagnosis of MTX-induced pneumonitis, which include: (1) acute onset of dyspnea; (2) fever  $> 38^{\circ}\text{C}$ ; (3) tachypnea; (4) radiological evidence of pulmonary interstitial or alveolar infiltrates; (5) white blood cell count  $< 15000/\text{cu mm}$ , with or without eosinophilia; (6) negative blood and sputum cultures (mandatory); (7) the finding of a restrictive pattern and decreased diffusing capacity of the lung for carbon monoxide (DLCO) on PFT; (8)  $\text{PO}_2 < 60$  mmHg on room air; and (9) histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection. MTX-induced pneumonitis is considered definite if  $\geq 6$  criteria are present, probable if 5 of 9 criteria are present, and possible if 4 of 9 criteria are present. Subsequently, new guidelines have been developed that include 3 major criteria, which are: (1) hypersensitivity pneumonitis by histopathology without evidence of a pathogenic organism; (2) radiologic evidence of pulmonary interstitial or alveolar infiltrates; and (3) negative blood and initial sputum cultures. The guidelines also include 5 minor criteria, which are (1) shortness of breath for less than 8 wk; (2) nonproductive cough; (3) oxygen saturation  $\leq 90\%$  on room air at the initial evaluation; (4) DLCO  $\leq 70\%$  of predicted for age; and (5) leukocyte count  $\leq 15000$  cells/cu mm<sup>3</sup>. The diagnosis is considered certain when a patient meets the first major criterion and at least 3 of the minor criteria, or when a patient meets major criteria 2 and 3 as well as 3 minor criteria. In this system, the diagnosis is considered probable when a patient meets only the major criteria 2 and 3 and 2 of the minor criteria<sup>[37]</sup>. Sidhu *et al.*<sup>[4]</sup> reported that chest X-ray findings included diffuse, bilateral, basal interstitial, or



alveolar infiltrates. The authors also observed that the most frequent radiographic pattern shown on HRCT of RA-ILD is the non-specific interstitial pneumonia (NSIP) pattern. MTX-associated pneumonitis is described as a type-IV delayed-hypersensitivity pneumonitis dominated by lymphocytic proliferation and alveolitis<sup>[38]</sup>; it is associated with a specific cellular immune response involving the release of cytokines<sup>[39]</sup>. Chikura *et al.*<sup>[40]</sup>, in a retrospective study, observed that the following two forms of ILD have been attributed to MTX. Type 1 MTX-related ILD appears shortly after treatment initiation (< 6 mo) and is characterized by neutrophil infiltration, lung fibrosis, lower time of MTX to low-dose exposure, and a high mortality rate. Type 2 MTX-related ILD occurs later in MTX treatment (> 6 mo) and is associated with lymphocyte-dominated infiltrates, low levels of lung fibrosis, a higher MTX dose exposure, and a low mortality rate. Type II pneumocyte hyperplasia and fibroblast proliferation have been reported as being suggestive of, but not pathognomonic for, MTX-induced lung toxicity<sup>[37]</sup>. A combination of a recent history of MTX initiation, clinical characteristics such as dyspnea, cough and fever, plus the findings of patchy ground-glass opacities on HRCT, increased lymphocytes and eosinophils in the BAL, and (if available) a lung biopsy showing interstitial pneumonitis with non-necrotizing granulomas and eosinophils, supports the diagnosis of MTX-induced ILD. To date, the optimal cost-effective strategy for detecting ILD changes in patients who are beginning MTX treatment has not been identified. Khadadah *et al.*<sup>[41]</sup> have suggested that periodic monitoring with PFT in patients with RA starting MTX therapy could be a rational strategy. Nevertheless, the findings of other authors do not support these recommendations. For example, Dawson *et al.*<sup>[42]</sup> did not observe differences in PFT or HRCT findings between patients with RA who had been treated with MTX versus other drugs, concluding that serial PFT in patients receiving MTX has no significant advantages. Therefore, there is presently no conclusive information about whether to perform PFT or HRCT in patients who are receiving MTX and do not have clinical symptoms or signs suggesting lung toxicity. However, the use of MTX in patients with pre-existing RA-ILD constitutes a significant risk factor for the development of pulmonary toxicity. Therefore, we recommend avoiding, if possible, the use of this drug in patients with a previous diagnosis of ILD. Other factors related to MTX-induced lung toxicity include elderly age, diabetes mellitus, and hypoalbuminemia, among others<sup>[43]</sup>. Once MTX-induced ILD is suspected, the treatment must include the immediate suspension of MTX and corticosteroid treatment, with the corticosteroid dosage depending on the severity of the lung involvement and other relevant clinical characteristics. In severe cases, supplementary oxygen, antibiotics or assisted ventilation should be considered. Once the patient is stabilized, MTX must be avoided, and alternative agents that do not increase the risk of

developing subsequent episodes of ILD should be considered. Among these options are the antimalarials. The prognosis of MTX-induced lung toxicity is usually good for the majority of patients, although a mortality rate of 13% has been reported in a review of MTX-induced pneumonitis in patients with a variety of different diseases (approximately 50% of whom had RA)<sup>[44]</sup>.

### **LFN and lung damage**

Establishing a clear association between LFN treatment and the development of ILD has been difficult, as LFN is frequently used after MTX failure; it can therefore be difficult to distinguish whether the development of ILD was secondary to LFN, MTX, or both drugs. Sawada *et al.*<sup>[45]</sup> analyzed the results of a cohort of 5054 Japanese RA patients and observed the development of ILD in 1.2% of patients. Suissa *et al.*<sup>[46]</sup> reported that LFN may enhance the risk of ILD by 1.9-fold. Chikura *et al.*<sup>[47]</sup> described, in a systematic review, that LFN-induced interstitial pneumonia occurs within the first 20 wk of LFN treatment initiation. Additionally, the authors reported a 19% mortality rate in patients with LFN-associated ILD. The factors associated with LFN-induced ILD were also analyzed by Sawada *et al.*<sup>[45]</sup> and included the use of LFN in patients with pre-existing ILD (OR = 8.17, 95%CI: 4.63-14.41,  $P < 0.001$ ), the use of an LFN loading dose (OR = 3.97, 95%CI: 1.22-12.92,  $P = 0.02$ ), cigarette smoking (OR = 3.12, 95%CI: 1.73-5.597,  $P = 0.001$ ) and low body weight < 40 kg (OR = 2.91, 95%CI: 1.15-7.37,  $P = 0.02$ ). Sato *et al.*<sup>[48]</sup>, in a retrospective study of patients with LFN-induced pulmonary injury, observed that an oxygen saturation level of < 90% is a marker for greater mortality in RA-ILD patients. The authors also found that serum C-reactive protein level were higher ( $P = 0.03$ ) and that the albumin level decreased ( $P = 0.03$ ) at the outset of lung injury in patients with fatal outcomes in comparison with patients who recovered. It is relevant to highlight that the main histopathological finding reported in this study in the two autopsied patients was diffuse alveolar damage (DAD), in contrast to the alveolitis with lymphocyte infiltration observed in patients who recovered. The mechanism of the development of ILD in patients exposed to LFN could be related to the effects of the active metabolite A771726, which induces the transition of lung epithelial cells to myofibroblasts<sup>[49]</sup>. In addition to other established therapeutic strategies for ILD, such as corticosteroids and (if required) mechanical ventilation, some authors recommend the immediate suspension of LFN and the addition of cholestyramine as wash-out therapy, constituting a rational intervention for these patients<sup>[50]</sup>.

### **Sulfasalazine and lung damage**

Numerous case reports have been published associating sulfasalazine (SSZ) with lung toxicity; a review of 50 cases<sup>[51]</sup> reported that most cases occurred

in patients with ulcerative colitis, although some cases were reported in RA patients. These authors noted that the clinical characteristics of SSZ-induced lung toxicity include dyspnea of recent onset that is associated with lung infiltrates and, in more than half of cases, with peripheral eosinophilia and a variable spectrum of pathological findings; the most common pathologic findings were eosinophilic pneumonia and interstitial inflammation in some patients with lung fibrosis. To date, it is not conclusively known which drug component is primarily responsible for lung toxicity, although it is believed that the major culprit is sulfapyridine. Once SSZ lung toxicity is suspected, the drug should be withdrawn immediately. Stopping the drug is followed by the rapid improvement of symptoms and signs of lung toxicity in most cases, although some patients with SSZ-induced lung toxicity may die, mainly if the drug is not withdrawn. Although a number of patients with SSZ-induced lung toxicity have been managed with corticosteroids, evidence for the benefit of corticosteroids in this setting is not definitive, and further studies are required.

#### **Azathioprine and lung damage**

Lung toxicity associated with azathioprine (AZA) has been observed primarily in patients with kidney transplants and may result from both allergic and dose-dependent toxicities. To date, there is only limited, case report-based information suggesting that AZA may induce lung toxicity in patients with previous ILD. Ishida *et al.*<sup>[52]</sup> reported the case of a male patient who developed interstitial pneumonia, was subsequently treated with AZA, and suffered worsening symptoms. The patient developed lung infiltrate and ground-glass opacities on lung HRCT after only 6 d of treatment with AZA. These pulmonary infiltrates resolved after the suspension of AZA treatment. As a small proportion of patients may die, physicians should be aware of this complication in patients who have initiated treatment with AZA and have a recent onset of cough, fever and dyspnea.

#### **Other synthetic disease-modifying antirheumatic drugs and lung damage**

Currently, gold salts and d-penicillamine are infrequently used to treat RA. Gold-induced lung damage is a challenging diagnosis in RA. Tomioka *et al.*<sup>[53]</sup> performed a review of published information regarding the clinical features and prognosis of gold-induced pulmonary disease in RA, identifying 140 cases of patients treated with gold, 81% of whom had RA. These authors reported that patients with gold-induced pulmonary damage frequently have other side effects associated with toxicity to gold salts, such as skin rash (38%), peripheral eosinophilia (38%), proteinuria (22%) and liver dysfunction (15%). In this review, factors frequently associated with gold-induced pulmonary disease included female sex, fever, skin rash, absence of rheumatoid nodules, low titers of rheumatoid factor,

lymphocytosis in BAL, and alveolar opacities along the broncho-vascular bundles visualized on chest computed tomography. Patients generally improve after withdrawal of the gold salts and may require treatment with corticosteroids. Currently, d-penicillamine is rarely used. Chakravarty *et al.*<sup>[54]</sup> reported that after 2 years of follow-up, 21% of their patients treated with d-penicillamine developed a restrictive pattern on PFT. Nevertheless, the incidence of severe pulmonary adverse reactions to d-penicillamine is relatively rare. Grove *et al.*<sup>[55]</sup> evaluated common adverse reactions to synthetic disease-modifying antirheumatic drugs (DMARDs) in 2170 patients with RA, who were followed for a total of 9378 treatment-years. Of these, 582 patients were exposed to d-penicillamine during a total of 1889 monitored treatment years. Although this was an important series of patients treated with d-penicillamine, the authors were able to find only one patient who stopped d-penicillamine due to a severe pulmonary reaction.

Regarding synthetic DMARD-induced ILD, it is important to take into account the following points: (1) the age-adjusted incidence of MTX-induced pneumonitis is approximately 3.78 cases per 1000 patients treated with MTX<sup>[56]</sup>; (2) factors associated with MTX-induced ILD include: male gender, impairment in functioning, and elevated ESR<sup>[56]</sup>; (3) the initiation of MTX treatment, along with clinical manifestations including dyspnea, cough, fever, and patchy ground-glass opacities on HRCT may suggest the diagnosis of MTX-induced ILD; (4) if MTX-induced ILD is suspected, the drug must be immediately discontinued; (5) the use of LFN increases the risk of ILD, which usually occurs within the first 20 wk after beginning this therapy<sup>[46,47]</sup>; (6) a relevant marker for mortality in LFN-induced ILD patients is a < 90% oxygen saturation level<sup>[48]</sup>; (7) patients with LFN-induced ILD must immediately stop treatment with LFN, begin corticosteroids, undergo mechanical ventilation if required, and receive cholestyramine wash-out treatment<sup>[50]</sup>; and (8) similar guidelines can be used to manage ILD induced by other synthetic DMARDs.

#### **Biologic agents and lung damage**

TNF- $\alpha$  inhibitors are commonly used for the treatment of RA and offer a good alternative in patients who have failed treatment with MTX or other synthetic DMARDs with high response rates. There are two major concerns with the use of anti-TNF agents and RA-ILD: (1) the possible association between the use of anti-TNF agents and the new onset of clinically significant ILD; and (2) the possibility of exacerbating preexisting ILD when an anti-TNF agent is used for controlling disease activity in RA (despite reports that treatment with anti-TNF agents may stabilize or improve ILD in some patients). The paradoxical effects of anti-TNF agents in ILD are interesting, and further studies are required to identify why some patients improve while others develop worsening disease. We will briefly review some of the evidence regarding ILD related to

the use of anti-TNF agents in RA.

Presently, there is increasing evidence suggesting that the use of TNF- $\alpha$  inhibitors is associated with the development of ILD. Ramos-Casals *et al.*<sup>[57]</sup>, in a case series of 233 patients treated with anti-TNF agents (71% of whom had RA), observed that 10% of patients developed ILD after initiation of anti-TNF therapy; the mean time for developing ILD after receiving anti-TNF drugs was 42 wk, and mortality was reported in 32% of patients with ILD.

There are a significant number of studies reporting the development of new cases of ILD or the worsening of pre-existing ILD following the use of anti-TNF agents, including infliximab<sup>[58-60]</sup>, etanercept<sup>[61-64]</sup>, and adalimumab<sup>[65-68]</sup>, as well as the newer anti-TNF agents such as golimumab<sup>[69]</sup> and certolizumab pegol<sup>[70-72]</sup>.

The development of ILD with etanercept treatment has been described in approximately 0.6% of patients (77 cases from 13894 patients treated with etanercept)<sup>[73]</sup>. For infliximab, one study<sup>[74]</sup> reported an incidence of 0.5% for ILD (25 cases of ILD from 5000 patients treated). In another study, the incidence of ILD in patients receiving tocilizumab was 0.48%<sup>[75]</sup>. However, for abatacept the incidence in one study has been reported to range from 0.1% (short-term) to 0.3% (long-term)<sup>[76]</sup>.

Perez-Alvarez *et al.*<sup>[77]</sup> analyzed 122 cases of new onset or exacerbated ILD secondary to biologic agents. Of these, 58 cases were observed in patients receiving etanercept and 56 cases in those treated with infliximab. The majority of these patients had RA. ILD developed at a mean of 26 wk after initiation of the biologic agent. Fifty-two patients had detailed follow-up; 29% died, 70% of these during the first weeks after the initiation of biologic agents.

Several mechanisms may explain the development of ILD associated with anti-TNF agents. It is unclear whether TNF blockers can potentiate the pulmonary toxicity of MTX<sup>[78]</sup>. However, some of these agents, such as infliximab, bind to TNF that is expressed on the surface of macrophages and CD4<sup>+</sup> and T cells, resulting in cell lysis<sup>[79]</sup>. It is thus conceivable that the local release of macrophage-derived proteolytic enzymes may contribute to MTX toxicity. Other potential mechanisms for the development or progression of ILD and lung fibrosis in some patients receiving anti-TNF agents may involve the down-regulation of TNF $\alpha$  (due to TNF blockade), which causes the up-regulation of anti-inflammatory cytokines including transforming growth factor  $\beta$ , leading to a profibrotic state<sup>[80]</sup>.

In the study by Perez-Alvarez<sup>[77]</sup>, patients with antecedents of ILD before being treated with biologic agents had a high mortality rate, which was associated with worsening ILD after the initiation of biologic therapy. Other factors associated with mortality were age > 65 years, later onset of ILD, and use of immunosuppressive drugs.

Ramos-Casals *et al.*<sup>[81]</sup> analyzed 379 cases of autoimmune diseases secondary to anti-TNF agents.

Using data obtained from the BIOGEAS project ([www.biogeas.org](http://www.biogeas.org)), a study with the aim of collecting data on the use of biological agents in patients with systemic autoimmune diseases, Ramos-Casals reported cases of ILD induced by biological agents. These authors described 34 patients who developed ILD after the initiation of anti-TNF agents, 30 of whom had RA. The most commonly used anti-TNF agents were infliximab in 20 cases (59%), etanercept in 11 cases (32%) and adalimumab in 3 cases (9%). Interestingly, although the majority of the patients had received MTX, 11/31 patients (35%) of these patients had no history of MTX use. The use of anti-TNF agents, particularly in the lung, has poor efficacy in controlling collagenosis-associated ILD and can lead to other complications, such as reactivation of mycobacterial and fungal infections, as well as to sarcoidosis and other ILD<sup>[81]</sup>.

Most recently, the rate of mortality has been evaluated in patients with RA who had ILD before beginning treatment with anti-TNF agents. The British Society for Rheumatology Biologics Register<sup>[82]</sup> followed 299 patients with pre-existing RA-ILD who were treated with anti-TNF agents, as well as 68 patients who were treated with synthetic DMARDs. In this cohort, 70/299 patients with pre-existing ILD who were treated with anti-TNF agents died, with RA-ILD being the underlying cause of death in 15/70 (21%) patients. However, 14/68 patients treated with synthetic DMARDs died; in only one patient (7%) was the cause of death related to ILD. Although the proportion of deaths attributable to RA-ILD in this study was higher in patients receiving anti-TNF agents, the authors recognized the possibility of reporting bias that may have influenced the validity of their results.

### **Other biologic agents associated with ILD**

To date, there has been one case report of a patient with RA who was treated with abatacept and developed worsening ILD<sup>[83]</sup>. Weinblatt *et al.*<sup>[76]</sup> analyzed the data from 8 clinical trials of abatacept in RA and observed a rate of 0.1% (2 cases of 3173 patients analyzed) for the development of ILD in the short-term period ( $\leq$  12 mo). This rate increased to 0.3% (11 cases of 4149 abatacept-treated patients) in the pooled long-term period.

Some isolated cases of new ILD or exacerbations of pre-existing ILD have been associated with the use of tocilizumab (TCZ). Kawashiri *et al.*<sup>[84]</sup> described an exacerbation of pre-existing ILD in a 68-year-man with RA after 10 mo of treatment with TCZ. This patient died despite treatment with pulsed-dose steroids and antibiotics. The main pharmacological agents related to ILD in RA patients are summarized in Table 3.

Some points to remember in ILD-associated biologic agents include the following: (1) the incidence of new-onset ILD with anti-TNF agents is low, and in some studies probably does not differ from the incidence observed with MTX<sup>[85]</sup>; (2) although a higher incidence of new-onset ILD is expected in RA patients

**Table 3 Pharmacological agents implicated in the development of interstitial lung disease in rheumatoid arthritis patients**

Pharmacological agent	Relevant information
DMARDs	
MTX	Long-term frequency of MTX-induced ILD is 0.43% <sup>[35]</sup>
	Incidence is 3.78/1000 patients <sup>[56]</sup>
LFN	Risk factor for ILD in RA patients (RR = 7.81) <sup>[33]</sup>
	Increases the risk of developing ILD <sup>[46]</sup>
	Mortality of 19% in patients with LFN-induced ILD <sup>[47]</sup>
AZA	Complication of interstitial pneumonia after treatment with AZA <sup>[52]</sup>
TNF- $\alpha$ inhibitors	Mortality is 32% in patients with ILD treated with TNF- $\alpha$ inhibitors <sup>[57]</sup>
Etanercept	Incidence of etanercept-induced ILD is 0.6% <sup>[73]</sup>
Infliximab	Incidence of infliximab-induced ILD is 0.5% <sup>[74]</sup>

DMARDs: Disease-modifying antirheumatic drugs; MTX: Methotrexate; ILD: Interstitial lung disease; RA: Rheumatoid arthritis; RR: Relative risk; LFN: Leflunomide; AZA: Azathioprine; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .

treated with anti-TNF agents (compared with other CTD that are also treated with anti-TNF therapy), this rate is approximately 7 times higher in RA compared with other diseases such as ankylosing spondylitis or psoriatic arthritis; (3) most reported cases of new-onset or worsening ILD with anti-TNF therapies are secondary to etanercept or infliximab<sup>[77]</sup>; (4) always suspect a worsening of ILD in patients with previous ILD who develop cough, dyspnea and fever; (5) most reported cases of new-onset ILD or worsening of a previous ILD appear in the first year after initiation of biologics; in one report, the mean was 26 wk<sup>[77]</sup>; (6) in patients with baseline (before treatment initiation) ILD, the mortality attributable to ILD in patients treated with anti-TNF agents is higher than those treated with synthetic DMARDs<sup>[82]</sup>; (7) characteristics supporting an association between ILD and treatment with biologics include recent initiation of therapy with a biologic agent, usually in elderly patients; most such patients show clinical improvement after the suspension of biologic agents and the addition of steroids; and (8) Treatment for patients with a suspicion for ILD induced or worsened by synthetic or biologic DMARDs should include the following elements: if there is a suspicion of drug-induced pulmonary damage, the agent must be rapidly discontinued; the use of other drugs that may potentially be implicated in lung damage should be avoided; smokers should stop smoking; patients may receive supportive therapy, such as supplementary oxygen, treatment of concurrent respiratory infection with antibiotics or mechanical ventilation, as indicated; and corticosteroids are the most commonly used drug for the management of drug-induced pulmonary damage and can be administered orally or intravenously at variable dosages. (In severe cases, prednisone should be administered at a dosage of 1 mg/kg. Other corticosteroids can be given at equivalent dosages, and, if required, a steroid pulse can be

used, particularly intravenous methylprednisolone at dosages of 1 g/d over 3 to 5 d). In patients with acute episodes, a clinical and symptomatic response can be observed around 24-48 h after withdrawal of the offending drugs. However, in cases of chronic damage, this response can be delayed.

One study<sup>[77]</sup> described response rates in 52 cases of biologic-associated ILD: complete resolution was achieved in 40%, improvement or partial resolution in 25%, and no resolution in 35%. In this study, 29% of patients died during follow-up, with 70% of deaths occurring during the first 5 wk after the development or worsening of a previous biologic-associated ILD.

### Importance of hepatitis C virus and lung damage in RA: Maillefert *et al.*<sup>[86]</sup>

observed that the prevalence of hepatitis C virus (HCV) in patients with RA was approximately 0.65% (taking into account both history of HCV or active infection) and did not differ from the prevalence of HCV infection in the general population. Nevertheless, HCV infection is relevant because patients with concurrent HCV and RA may have an increased prevalence of lung damage. Aliannejad *et al.*<sup>[87]</sup> in a review, observed a discrepancy between studies evaluating the frequency of HCV in idiopathic pulmonary fibrosis (IPF) patients, which might be attributed to geographical differences for the prevalence of HCV infection or selection bias in choosing the control group. HCV infection is associated with increased counts of lymphocytes and neutrophils in BAL fluid. These studies have shown that HCV infection is associated with nonspecific pulmonary inflammatory reactions that lead in some patients to pulmonary fibrosis. The treatment of HCV infection, especially with interferon therapy, has also been implicated in the development of lung damage in HCV patients. Complications associated with INF therapy include interstitial pneumonia and pulmonary sarcoidosis. Ueda *et al.*<sup>[88]</sup> reported a higher prevalence of HCV antibodies in patients with IPF (28.8%) compared with that observed in age-matched control subjects (3.6%). Ferri *et al.*<sup>[89]</sup>, in a cohort of 300 HCV-positive patients, observed eight patients with interstitial lung involvement. In 6 patients, the presence of lung involvement was suspected on the basis of dyspnea with dry cough or digital clubbing. Different degrees of reduction in DLCO were observed; spirometric abnormalities, consistent with a global restrictive pattern, were found less frequently. The presence of parenchymal radiotracer uptake on G67 scan and an increased percentage of neutrophils and lymphocytes on BAL suggested active lung involvement. The treatment of HCV infection is associated with decreased pulmonary function. Foster *et al.*<sup>[90]</sup> reported the results of a controlled clinical trial of 391 patients with HCV infection who received 24 wk of treatment with alb-IFN- $\alpha$ -2b or pegylated IFN- $\alpha$ -2a (peg-IFN $\alpha$ -2a) and ribavirin. Patients were followed over 6 mo with spirometry, DLCO, and chest



**Table 4** Histological and clinical classification of idiopathic interstitial pneumonias

Histologic pattern	Clinical-Radiological-Pathological Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/COP
NSIP	NSIP
Organizing pneumonia	COP
Diffuse alveolar damage	Acute interstitial pneumonia
LIP	LIP

From: ref.<sup>[107]</sup>, American Thoracic Society; European Respiratory Society. *Am J Respir Crit Care Med* 2002; 165: 277-304. COP: Cryptogenic fibrosing alveolitis; NSIP: Non-specific interstitial pneumonia; LIP: Lymphoid interstitial pneumonia.

X-ray. During follow-up, DLCO declines of < 15% were observed in 173 (48%) of patients, whereas one patient developed new interstitial chest X-ray abnormalities. The underlying mechanisms for this decline in pulmonary function in patient's treatment with alb-IFN- $\alpha$ -2b or pegylated IFN- $\alpha$ -2a require further investigation.

## BIOMARKERS FOR RA-ILD

To date, the use of RF and anti-CCP as predictive biomarkers for ILD development in patients with RA remains controversial. Some evidence indicates that there is a clear association between high RF and anti-CCP titer levels and RA-ILD<sup>[29]</sup>. However, other authors have not identified an association between anti-CCP and RA-ILD<sup>[31]</sup>.

In serum from patients with RA-ILD, Harlow *et al*<sup>[91]</sup> identified citrullinated heat shock proteins (Hsp) 90 $\alpha$  and Hsp90 $\beta$  as potential biomarkers for ILD in patients with RA (Sensitivity, 0.29; Specificity, 0.96). Serum ferritin has been proposed as a prognostic marker in scleroderma-ILD based on the finding that patients with higher ferritin levels at baseline (> 1500  $\mu$ g/L) had a significantly increased risk of fatal outcomes<sup>[92]</sup>. To date, there has been a lack of information about serum ferritin in RA-ILD. However, in a cross-sectional study, Rosas *et al*<sup>[93]</sup> observed significantly increased matrix metalloproteases (MMP)-7 and MMP-1 concentrations in the serum of patients with IPF ( $P = 0.01$  and  $P < 0.001$ , respectively). Additionally, the authors reported that a combination of enhanced concentrations of MMP-7 and MMP-1 could discriminate IPF from hypersensitivity pneumonitis, with a sensitivity of 96.3% and a specificity of 87.2%<sup>[93]</sup>. Further studies of these metalloproteases in RA-ILD are required.

Ascherman *et al*<sup>[94]</sup> reviewed potential biomarkers implicated in RA-ILD. To date, the following cytokines have been considered as potential biomarkers of ILD: platelet derived growth factor isoforms AB and BB, interferon-alpha, and profibrotic cytokine transforming growth factor-B1. Elevated levels of these cytokines have been observed in BAL. High levels of Krebs von den Lungen-6 protein (KL-6) have been identified

in serum, reflecting alveolar damage. KL-6 protein levels have demonstrated a correlation with the severity of ILD, as evaluated by HRCT<sup>[95]</sup>. The role of other potential biomarkers, such as surfactant protein-D (SP-D), surfactant protein-A (SP-A), and YKL-40 chitinase-3-like protein 1, or cytokines such as chemokine motif ligand 18, which have been identified in other CTD complicated by lung involvement, should be evaluated in RA-ILD<sup>[96]</sup>.

## HISTOPATHOLOGY

Five main histological patterns of ILD have been characterized, including NSIP, usual interstitial pneumonia (UIP), DAD, organizing pneumonia (OP), and lymphocytic interstitial pneumonia (LIP)<sup>[97]</sup>. The histological patterns of ILD and their relationship to clinical and radiological features are summarized in Table 4. The most frequent histological pattern of RA-ILD is UIP, followed by NSIP. In terms of severity, Kim *et al*<sup>[98]</sup> reported in 2010 that the UIP pattern in RA-ILD was associated with worse survival than the non-UIP pattern. In patients with UIP, the mean survival was 3.2 years; in patients with the non-UIP pattern, mean survival time was 6.6 years ( $P = 0.04$ ). The severity and high mortality of the DAD pattern has been recognized. Tsuchiya *et al*<sup>[99]</sup> reported that patients with the DAD histological pattern of RA-ILD had the highest mortality, with a median survival time of 0.2 years.

## DIAGNOSIS

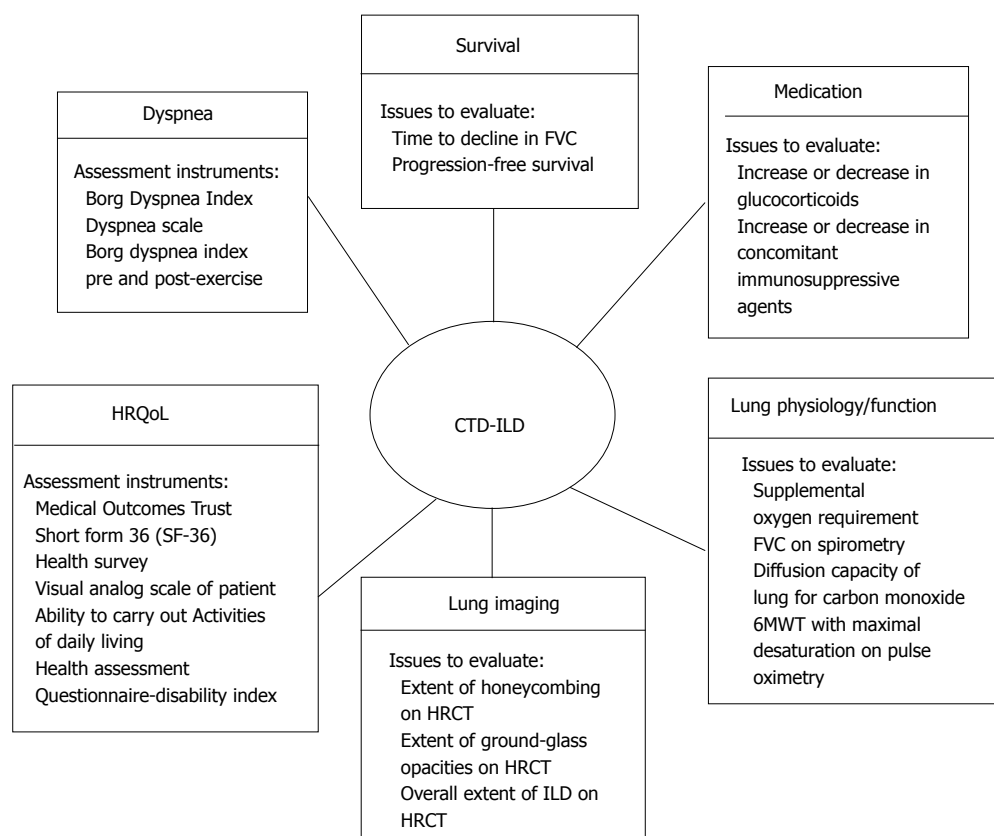
### Clinical features

The clinical symptoms of RA-ILD are non-specific. Dyspnea on exertion is the most frequent symptom, and cough, sputum production, wheezing, and chest pain have also been reported<sup>[100]</sup>. However, dyspnea and physical limitations may not be apparent in the early stages of disease.

### Core set of domains in clinical trials

Using Delphi and nominal group techniques, a group of experts recently proposed a preliminary core set of outcome measures in connective tissue disease-associated ILD (CTD-ILD) and idiopathic pulmonary fibrosis for use in clinical trials<sup>[101]</sup>. The results of this study included identification of the following domains to be measured in clinical trials: (1) dyspnea; (2) health-related quality of Life (HRQoL); (3) lung imaging; (4) lung physiology/function; (5) survival; and (6) medications.

The instruments accepted for each domain were derived from the Delphi Technique and are depicted in Figure 1<sup>[101]</sup>. Selection of this core of domains and instruments is very useful in diverse contexts in order to standardize the assessment of clinical responses across studies, rendering these results useful for systematic reviews or meta-analyses, and to facilitate



**Figure 1** Suggested instruments to assess connective tissue disease associated interstitial lung disease, based on the Delphi Technique<sup>[101]</sup>. CTD-ILD: Connective tissue disease associated-interstitial lung disease; FVC: Forced vital capacity; HRQoL: Health-related quality of life; HRCT: High-resolution computed tomography.

the selection of outcome measures in multicenter randomized controlled trials.

The treatment of RA-ILD can be classified into supportive measures and treatment against the inflammatory processes that are responsible for ILD. To date, there is no specific treatment for RA-ILD. The best therapeutic strategy is believed to be a multidisciplinary approach that evaluates the severity of lung involvement, the type of pneumonitis, concomitant organs involved, and associated comorbidities. At our center, this therapeutic approach is performed by a rheumatologist, a pulmonologist, and a specialist in internal medicine. Included among supportive measures are supplementary therapy with oxygen, pulmonary rehabilitation, anti-reflux therapy, and treatment of comorbidities<sup>[102]</sup>. Many patients may have coexisting infections, and appropriate antimicrobial agents should be considered in such cases.

### Six-minute walk test

The six-minute walk test (6MWT) measures the distance that a patient can walk quickly on a flat, hard surface over a period of 6 min (6MWD). It evaluates the global and integrated responses of all of the systems involved in exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units,

and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or on the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing<sup>[103]</sup>. Changes in 6MWD after therapeutic interventions correlate with subjective improvements in dyspnea<sup>[104]</sup>.

### St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire was originally developed to assess the health status of patients with chronic obstructive pulmonary disease and asthma<sup>[105]</sup>. It has also been used for patients with other diseases, such as bronchiectasis and ILD<sup>[106]</sup>. Chang *et al.*<sup>[106]</sup> observed that forced vital capacity (FVC)% was more strongly correlated with activity score than with symptom score. Similarly, on the chronic respiratory questionnaire, the dyspnea score was significantly correlated with FVC%, whereas the fatigue and emotional scores were not correlated.

### PFT

Patients with RA-ILD usually demonstrate a restrictive pattern on PFT with reduced total lung capacity (TLC), or a diminished FVC with a normal or increased forced expiratory volume at 1 second/forced vital capacity (FEV1/FVC) ratio and/or impaired gas exchange, which is characterized by an increased P (A-a) O<sub>2</sub> (Alveolar-

arterial pressure difference for O<sub>2</sub>), decreased PaO<sub>2</sub> at rest or exertion, or decreases in the DLCO<sup>[107]</sup>. Chen *et al*<sup>[10]</sup> observed, in a cross-sectional study of patients with RA-ILD, the presence of severe respiratory impairment [lower percent predicted FVC (74.9 ± 12.2 vs 86.9 ± 11.3; *P* < 0.001), TLC (87.8 ± 15.7 vs 98.4 ± 11.3; *P* = 0.001), FEV1 (74.1 ± 14.6 vs 88.0 ± 12.9; *P* < 0.001), and DLCO (68.1 ± 19.5 vs 96.2 ± 17.7; *P* < 0.001)] compared to RA patients without ILD. Saag *et al*<sup>[14]</sup>, in a cross-sectional study, found that worse functioning as evaluated by the Health Assessment Questionnaire Disability-Index (HAQ-DI), was a risk factor for declines in both the DLCO and FVC. However, Kim *et al*<sup>[98]</sup>, in a retrospective study, observed that variables associated with a decrease in survival time in patients with RA-ILD included baseline FVC (HR = 0.98; *P* = 0.01), baseline DLCO (HR = 0.97; *P* = 0.002), and the presence of a UIP pattern on HRCT (HR = 2.09; *P* = 0.04).

### Radiological findings

Radiographically, changes observed in RA-ILD are indistinguishable from those observed in IPF or ILD associated with other connective-tissue diseases. Plain chest X-rays mainly demonstrate reticular and fine nodular opacities. These findings are commonly concentrated in the lower lung zones. Early on, these changes may appear as a patchy, alveolar-filling infiltrate. Disease progression results in a more reticulonodular pattern. Plain chest X-ray is an insensitive means for identifying ILD, which has a prevalence rate of only 6%<sup>[9]</sup>. Progression to nodular, patchy infiltrates may develop. Rarely, lymphadenopathy, rheumatoid nodules, and pleural effusions may be present<sup>[107]</sup>. Gabbay *et al*<sup>[9]</sup>, in a cross-sectional study, observed the prevalence of RA-ILD (14%) by employing a number of sensitive techniques in patients with RA for < 2 years.

### High resolution computed tomography and histological correlation

One of the varied manifestations of ILD is asymptomatic disease that is detected by HRCT of the chest and PFT<sup>[108]</sup>. The American Thoracic Society and the European Respiratory Society (ATS/ERS), in collaboration with the Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT), published HRCT criteria for the diagnosis of UIP. The following are the main criteria for UIP in HRCT (all four features must be present): subpleural, basal predominance; reticular abnormality; honeycombing with or without traction bronchiectasis, and the absence of features listed as inconsistent with the UIP pattern. The criteria for possible UIP pattern include all features for the UIP pattern listed above, except for honeycombing. Inconsistent with the UIP pattern are any of the following seven features: upper or mid-lung predominance; peribronchovascular predominance; extensive ground-glass abnormality (extent >

reticular abnormality); profuse micronodules (bilateral, predominantly upper lobes); discrete cysts (multiple, bilateral, at a distance from areas of honeycombing); diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes); and consolidation in bronchopulmonary segment(s)/lobe(s)<sup>[109]</sup>.

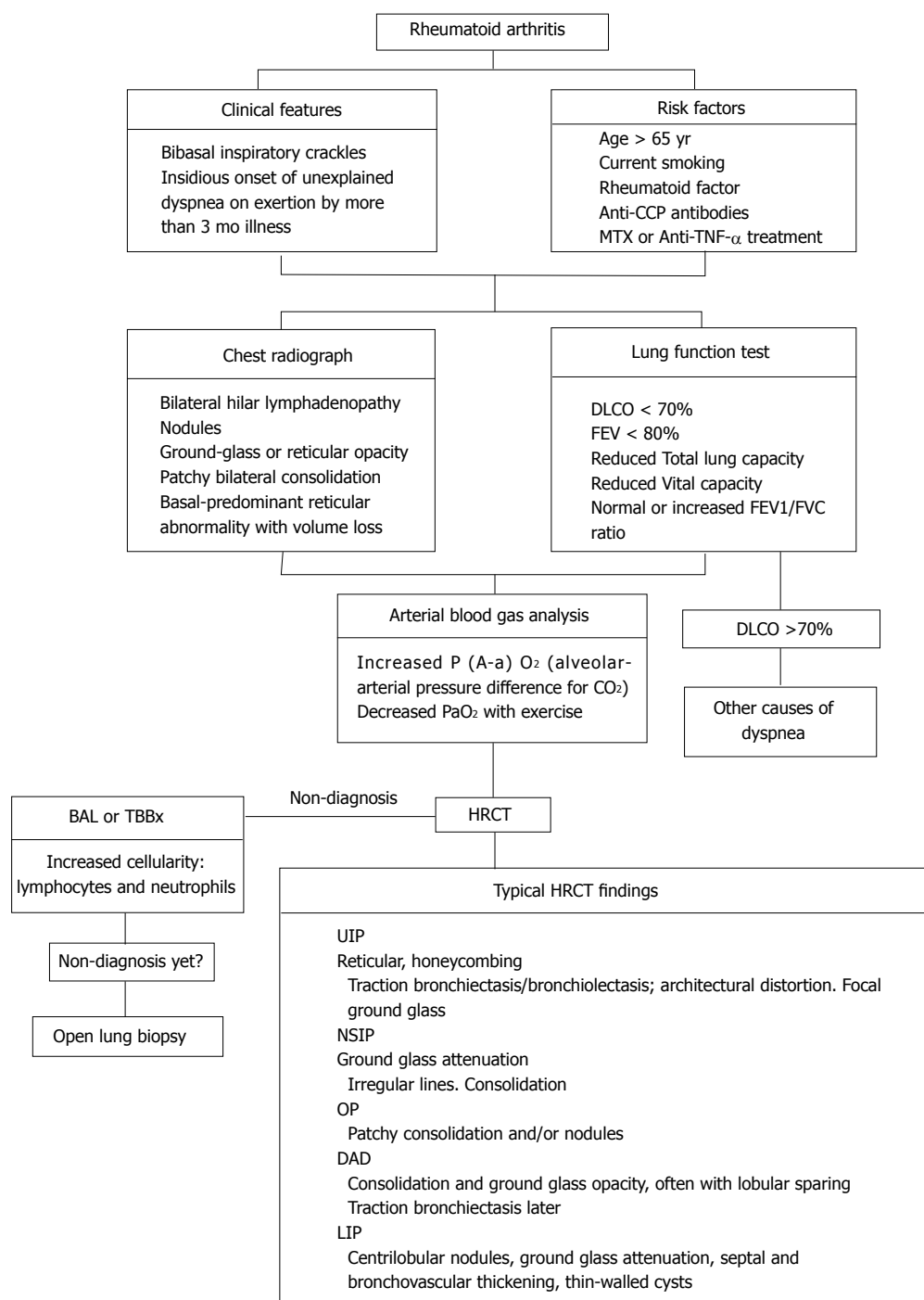
Assayag *et al*<sup>[110]</sup> compared, in a cohort of 69 patients with RA-ILD, the usefulness of two computed tomography (CT) criteria and their correspondence with histopathologic patterns. Using the strict criteria, a definite UIP pattern on a CT scan had 96% specificity with histopathological findings and a positive predictive value of 95%. However, the sensitivity of the UIP pattern on CT scan was 45%, and when the broad criteria were used, the sensitivity of CT scan increased to 81%, with a decrease in specificity to 85%. Kim *et al*<sup>[98]</sup>, in a retrospective study that included bivariate survival analysis of specific HRCT features in patients with RA-ILD, found that reticulation, traction bronchiectasis, and honeycombing were significantly associated with worse survival time. Cox regression modeling found that the presence and extent of traction bronchiectasis were significant independent predictors of worse survival time, with a hazard ratio (HR) 2.6; honeycombing had a HR for death of 2.1.

Pérez-Dórame *et al*<sup>[111]</sup> observed, in a cross-sectional study, the likelihood of NSIP being the most prevalent pattern on HRCT scans (29%). UIP patterns were observed in 13% of the patients. However, there was considerable overlap among tomographic patterns: 42% of patients had two ILD tomographic patterns, and 20% of patients also had small airway disease, defined as the presence of mosaic attenuation and air-trapping images.

### Correlation between PFT and HRCT

McDonagh *et al*<sup>[112]</sup>, in a cross-sectional study, calculated the sensitivity and specificity of PFT, using HRCT as the gold standard. These authors observed that reduced FEV and low total lung capacity (TLC) [both > 1 Standard (SD) deviation below that predicted] were highly sensitive markers for the presence of ILD on HRCT (88% and 90%, respectively). However, the specificity of each was relatively low (59% and 71%, respectively). The most sensitive test appeared to be measurement of residual volume (RV). A reduction of > 1 SD below the predicted RV was 83%- specific for ILD.

Figure 2 describes a diagnosis strategy for patients with suspicion of RA-ILD. This strategy is based on the findings of clinical features and/or presence of risk factors for ILD in patients with a recognized RA. A recommendation is to perform a systematic assessment of the arterial blood gas, PFT and chest radiograph. If there is evidence in any of these tests that justify further investigation, we recommend a HRCT as the next step. HRCT may exclude or confirm the diagnosis of ILD, nevertheless in case of a reasonable suspicion justified by the clinical findings



**Figure 2 Recommendations for the diagnosis of interstitial lung disease in rheumatoid arthritis patients.** Anti-CCP: Anti-cyclic citrullinated peptide; MTX: methotrexate; Anti-TNF- $\alpha$ : Anti-tumor necrosis factor- $\alpha$ ; DLCO: Diffusing capacity of the lung for carbon monoxide; FEV: Forced expiratory volume; FVC: Forced vital capacity; BAL: Bronchoalveolar lavage; TBBx: Transbronchial lung biopsy; HRCT: High-resolution computed tomography; UIP: Usual interstitial pneumonia; NSIP: Non-specific interstitial pneumonia; OP: Organizing pneumonia; DAD: Diffuse alveolar damage; LIP: Lymphocytic interstitial pneumonia.

with a HRCT that is not conclusive, probably invasive approaches, such as BAL or open lung biopsy should be considered.

### Positron emission tomography and interstitial lung disease

HRCT is an exclusively structural imaging technique from which only indirect inferences in relation to metabolism can be made. Recent technologic advances have led to the integration of positron emission

tomography (PET) with CT, allowing molecular imaging to be combined with the fine structural detail of CT. PET/CT has profoundly affected the management of cancer<sup>[113]</sup>. However, to date, PET/CT has not been used in patients with IPF and ILD<sup>[114]</sup>. PET with [18F]-Fluorodeoxyglucose ([18F]-FDG) can be used to quantify pulmonary inflammation. [18F]-FDG, a glucose analog, is taken up by the same transporters that take up glucose into the cell; therefore, [18F]-FDG uptake tracks cellular glucose transport, which



is highly correlated with the rate of cellular glucose metabolism<sup>[115]</sup>. Increased pulmonary [18F]-FDG metabolism in all patients with IPF and other forms of diffuse parenchymal lung disease was observed. Pulmonary 18F-FDG uptake predicts measurements of health and lung physiology in these patients. 18F-FDG metabolism was higher when the site of maximal uptake corresponded to areas of reticulation/honeycombing on HRCT, rather than to areas with ground-glass patterns. To date, there are, to our knowledge, no studies evaluating lung metabolism in patients with RA-ILD, and longitudinal studies evaluating treatment based on pulmonary metabolism are required.

## PULMONARY ARTERIAL HYPERTENSION AND RA-ILD

Pulmonary arterial hypertension (PAH) may be an extra-articular manifestation of RA or may be associated with RA-ILD<sup>[116]</sup>. PAH in patients with RA-ILD who have either dyspnea or lung dysfunction [reduced carbon monoxide transfer factor (TLCO) or desaturation on exercise] can appear disproportionate to the extent of parenchymal lung disease. Trans-thoracic echocardiography is a suitable screening tool for detection of pulmonary hypertension in patients with ILD<sup>[102]</sup>, and PAH can be confirmed with cardiac catheterization.

## PHARMACOLOGICAL TREATMENT

There is only limited information derived from well-designed clinical trials or prospective cohort studies regarding the efficacy of immunosuppressive or biological therapy for RA-ILD. Current understanding suggests that the therapeutic response depends on several factors, such as early detection of involvement, the radiological-histological subset (with lower rates of therapeutic response in fibrotic UIP compared with *Bronchiolitis obliterans* organizing pneumonia and non-fibrotic NSIP), and other comorbidities such as renal failure. There are several common clinical scenarios. The first scenario is an asymptomatic patient in whom ILD is discovered incidentally. In this patient, the decision to start treatment is not always easy, because ILD may remain stable in some of these patients for years, and aggressive therapy may cause severe, life-threatening side effects. On the other hand, an incidental finding of ILD represents a window of opportunity for initiating treatment prior to clinical worsening. In this scenario, patients should initially be closely monitored monthly, and thereafter, at 3-6 mo intervals with PFT and 6MWT; in case of deterioration, immunosuppressive therapy should be considered. The second scenario is that of a patient with symptoms and clinical signs of ILD and a confirmed diagnosis based on PFT and HRCT. In these patients, immunosuppressive therapy against the inflammatory

process should be initiated. The third scenario involves a patient who has failed treatment with immunosuppressive drugs, has severe lung fibrosis, and has very few or absent signs of inflammation on HRCT. These patients generally do not benefit greatly from immunosuppressive therapy. If, after a course of corticosteroids and immunosuppressive drugs, such patients suffer rapid deterioration of FVC, diffuse PaO<sub>2</sub> capacity of the lung for carbon dioxide (DLCO<sub>2</sub>), or clinical parameters, other therapies including lung transplantation should be considered (see later). In patients with moderate or severe symptoms and who have rapid progression of ILD (as reflected by a rapid deterioration of FVC and DLCO<sub>2</sub> with an increase in dyspnea), corticosteroids are considered first-line treatment.

However, there is a lack of evidence from controlled studies regarding the effect size of corticosteroid treatment on the therapeutic response in RA-ILD. This lack of clinical trials is explained because ILD is a life-threatening complication and ethically is not suitable for evaluation in placebo-controlled trials. One of the most recent studies evaluating the effect of corticosteroids on the therapeutic response was performed by Rojas-Serrano *et al.*<sup>[117]</sup>. These authors, in a retrospective cohort design of 40 patients with RA-ILD treated with prednisone 1 mg/kg per day for 6 wk followed by tapering of 10 mg/d for approximately 6–8 mo, observed significant improvement in FVC at the final evaluation (compared with baseline values). However, the lack of a comparison group and the fact that the majority of these 40 patients with ILD concomitantly received MTX, AZA, or LFN limit the study's usefulness in understanding the true effect of corticosteroids in these patients.

### Ineffective agents

Some medications have been used in CTD-ILD but have not demonstrated significant efficacy. These drugs include d-penicillamine and colchicine, which have been tested in systemic sclerosis but not in RA-ILD<sup>[118,119]</sup>. In an original study, Steen *et al.*<sup>[118]</sup> evaluated the effects of d-penicillamine in 44 patients with systemic sclerosis compared with patients who did not receive this drug; while patients who received d-penicillamine had no further progression of dyspnea or fibrosis in chest X-rays during follow-up, there were no significant modifications in vital capacity (VC). In an open trial, van der Schee *et al.*<sup>[120]</sup> evaluated the effects of d-penicillamine (750 mg/d) in seven patients with ILD-RA. Patients also received prednisone 60 mg/d during month 1 with a gradual taper; VC and CO diffusion were measured prior to treatment, at 1 mo, and annually. Anecdotal reports have described some cases of patients with ILD-RA who exhibited improvement after receiving cyclosporine<sup>[121]</sup>.

### Immunosuppressive agents

**Azathioprine:** Since the late 1970s, azathioprine and

corticosteroid therapy have been used for the treatment of RA-ILD in order to improve functional parameters and to stabilize lung inflammation. Cohen *et al.*<sup>[122]</sup> published one of the first case reports, which discussed a patient with RA-ILD who had been treated for 5 years with azathioprine; improvements in pulmonary function and clinical symptoms were observed. Interestingly, there is also a lack of evidence from controlled studies regarding the efficacy of azathioprine in RA-ILD.

**Cyclophosphamide:** Cyclophosphamide (CYC) is an immunosuppressive drug commonly used to treat patients with ILD. A recent study<sup>[123]</sup> evaluated the effects of CYC on serum and bronchoalveolar lavage (BALF), TNF- $\alpha$ , TGF- $\beta$ 1, and MMP-9 levels, as well as TNF- $\alpha$  and TGF- $\beta$ 1 messenger RNA (mRNA) levels, in the peripheral blood of patients with primary Sjögren's syndrome with ILD. The results of this study showed that TNF- $\alpha$ , TGF- $\beta$ 1, and MMP-9 levels decreased significantly after CYC treatment.

The majority of evidence published on CYC in ILD has been derived from patients with systemic sclerosis who were treated with CYC. Although CYC is the "gold standard" immunosuppressant for the treatment of CTD-ILD, a meta-analysis<sup>[124]</sup> evaluating the evidence of three randomized clinical trials and six prospective cohorts evaluating the effect of CYC on systemic sclerosis and ILD did not observe significant changes in the FVC or DLCO after 12 mo of therapy, concluding that CYC treatment did not result in a clinically significant improvement of pulmonary function in these patients. However, when the individual studies are examined, there was wide variability in CYC doses and administration, with some studies evaluating oral CYC whereas others employed intravenous (*iv*) administration. The studies also differ in concurrent interventions; patients in some studies also received high doses of corticosteroids, others low corticosteroid doses, and in one study, corticosteroids were not used. Therefore, new studies with similar designs, inclusion criteria, and concurrent interventions are required to support the results of this meta-analysis. CYC therapy has also been used in patients with suspected drug-induced ILD. In a case report, an RA patient with MTX-induced pneumonitis was considered resistant to withdrawal of MTX, oxygen administration, and pulse-dose corticosteroids. This patient was treated with an *iv* CYC pulse, resulting in a substantial improvement in hypoxemia and X-ray findings. The authors suggest that CYC should be considered in patients with MTX-induced pneumonitis without response to corticosteroids<sup>[125]</sup>.

**Mycophenolate mofetil:** Mycophenolate mofetil (MMF) has been studied in patients with CTD-ILD. In a case series<sup>[126]</sup>, 10 patients with autoimmune disorders complicated by ILD (three of whom had RA) received MMF. Symptomatic improvement was observed in 10/11 patients, and 4/5 discontinued oxygen. There

was stabilization or improvement in HRCT lesions in 8/8 patients, only 1/9 had worsening PFT, and patients were able to significantly decrease the dose of prednisone. The authors concluded that MMF is probably safer and more effective than CYC and should be considered as a first-line agent or a maintenance therapy after CYC treatment. However, these data are very preliminary and require corroboration in a controlled study that compares CYC vs MMF in ILD-RA.

**Combined therapy with methylprednisolone pulses:** Combined therapy with methylprednisolone and CYC has been evaluated mainly in patients with systemic sclerosis-associated ILD. Yiannopoulos *et al.*<sup>[127]</sup> evaluated 13 patients with systemic sclerosis-associated ILD, observing that 66.6% had stable or improved pulmonary function parameters. However, ILD worsened in some individuals after stopping treatment. The authors concluded that this combination is effective and well-tolerated and helps to stabilize respiratory function in ILD. Airò *et al.*<sup>[128]</sup> described the results of an observational study evaluating the results of the combination of CYC and 6-methylprednisolone in 13 patients with systemic sclerosis and active alveolitis, observing an increase in FVC ( $P = 0.005$ ) at 6 mo compared to baseline.

### Biologic agents

**Tocilizumab:** Tocilizumab is an interleukin (IL)-6 receptor blocker useful in the treatment of joint symptoms and some systemic manifestations in RA. Excessive production of IL-6 is associated with fibrosis in ILD; therefore, IL-6 constitutes a potential target in the treatment of RA-ILD. Gallelli *et al.*<sup>[129]</sup> have observed, in an *in vitro* study that used primary cultures of normal and fibrotic human lung fibroblasts, that the proliferative mechanisms induced by TGF- $\beta$ 1 are in part mediated by an increased release of IL-6, leading to phosphorylation-dependent mitogen-activated protein kinase (MAPK) activation. These findings help to understand the effects of therapies that are based on IL-6 inhibition and their effects on lung fibroblasts. Mohr *et al.*<sup>[130]</sup> described the results of tocilizumab in one patient with ILD-RA, observing an improvement in alveolitis and ground-glass opacities. Although the existing evidence is clearly insufficient to establish strong conclusions, it indicates the necessity of performing controlled studies to evaluate the efficacy of tocilizumab in these patients.

**Anti-TNF agents and ILD:** Only few case reports and case series have been published regarding patients with RA-ILD who may have benefited from anti-TNF treatment. Bargagli *et al.*<sup>[131]</sup> described the case of one patient with RA and pulmonary fibrosis, refractory to corticosteroids and azathioprine, who was treated with infliximab. These authors observed an improvement in vital capacity, TLCO and FEV1 after 15 mo of infliximab therapy. Similarly, Vassallo *et al.*<sup>[132]</sup>

described a response to infliximab in a patient with RA and pulmonary fibrosis refractory to corticosteroids. After 12 mo of infliximab treatment, this patient had symptomatic improvement with stabilization of PFT. Additionally, Antoniou *et al.*<sup>[133]</sup> identified responses to infliximab in a case series of 4 patients with CTD-associated pulmonary fibrosis (3 with RA and 1 with systemic sclerosis). The authors observed a stabilization of pulmonary fibrosis in terms of PFT results and HRCT findings after at least 12 mo of treatment. Etanercept is another anti-TNF agent where a therapeutic response in ILD has been observed. Schultz *et al.*<sup>[134]</sup> described a girl with juvenile chronic arthritis and pulmonary interstitial and intra-alveolar cholesterol granulomas, in whom treatment with etanercept improved symptoms and physical capacities. Wang *et al.*<sup>[135]</sup> described a therapeutic response to etanercept in a 52-year-old woman with RA-ILD that was refractory to corticosteroids and azathioprine. These authors observed a sustained improvement in symptoms, PFT results, and HRCT findings.

There is controversy concerning whether anti-TNF agents are associated with an increase in the prevalence of RA-ILD, and several case reports have been published on the development of RA in patients receiving anti-TNF agents<sup>[65,66,70-72,136]</sup>. In addition, cases have also been reported of patients with RA-ILD experiencing exacerbations of lung disease after receiving anti-TNF therapy<sup>[61]</sup>. Perez-Alvarez *et al.*<sup>[77]</sup> analyzed 122 cases of new-onset ILD or exacerbation of ILD in connective tissue diseases after administration of biological agents. Among these, 108 (89%) patients had RA. The drugs that were most frequently associated with ILD were etanercept (58 patients) and infliximab (56 patients); ILD developed at a mean of 26 wk after starting biological agents.

**Rituximab:** B cells are probably involved in the pathogenesis of RA-ILD. Atkins *et al.*<sup>[137]</sup> have observed the presence of follicular B-hyperplasia and infiltration of the interstitium with plasma cells in patients with interstitial pneumonia. Observational and open uncontrolled studies have described the effects of rituximab (RTX) in patients with RA-ILD. Matteson *et al.*<sup>[138]</sup> described the effects of RTX (1000 mg given on day 1 and day 15 and again after 24 and 26 wk) on 10 patients with RA-ILD who were evaluated in a 48-wk, open clinical trial. At the end of the study, only 7/10 patients were assessed for therapeutic response. Among these patients, DLCO<sub>2</sub> increased > 15% of baseline in 2/7 patients, remained stable in 4/7 patients, and worsened in 1/7 patients. However, the FVC increased by at least 10% in 2/7 patients, was stable in 4/7 patients, and declined in 1/7 patients. In the six patients who had a follow-up HRCT, findings remained unchanged in 5/6 and improved in 1/6. These preliminary data suggest that RTX benefits only some patients with RA-ILD; nevertheless, further controlled studies are required to identify the possible

effects of RTX on patients with established RA-ILD. Dass *et al.*<sup>[139]</sup> described the safety of RTX among 67 patients with RA and lung involvement; of these, 48 patients (71.6%) had ILD. The authors observed 3 deaths (2 patients with ILD and 1 patient with chronic obstructive pulmonary disease), one of which was secondary to pneumonia and acute progression of ILD observed in the 4 wk after the first cycle of RTX. These authors conclude that treatment with RTX in patients with RA and lung involvement apparently does not increase the rate of expected severe side effects.

Romero *et al.*<sup>[140]</sup> described the safety of RTX in a series of 14 patients with CTD-ILD, 29 of whom had RA-ILD. They observed a decreased incidence of ILD relapse during rituximab therapy (0.745/100 patient-months) compared to 5.56/100 patient-months during the pre-treatment period. Only 12 patients had PFT results available during follow-up, demonstrating an increase in FVC and DLCO. Radiographic studies were available in 6 patients and demonstrated stabilization of ILD in 5/6 and improvement in 1/6. These authors conclude that RTX was safe in the sample studied, although there was 1 death secondary to neutropenia and a disseminated fungal infection during follow-up. Becerra *et al.*<sup>[141]</sup> described the results of treatment with RTX in 38 patients with RA and lung involvement, 19 of whom had ILD. They observed that lung disease remained stable, although one patient with severe UIP developed progressive lung disease. Interestingly, 66% of the patients had respiratory infections, 2 of which required hospitalization. There were 2 deaths in this series, neither of which was related to RTX treatment. These authors conclude that RTX is a relatively safe therapy in patients with RA and lung involvement; however, there is no significant evidence to demonstrate improvement in lung disease.

**Abatacept:** Abatacept is a promising biologic agent for RA; nevertheless, there is a lack of studies evaluating the safety of abatacept in RA-ILD, and most information about this medication has been obtained from observational studies, particularly case reports. In a mice model of hypersensitivity pneumonitis characterized by T cell-mediated lung inflammation, the administration of abatacept significantly decreased the extent of lung damage and decreased the number of inflammatory cells in the BAL<sup>[142]</sup>. Wada *et al.*<sup>[83]</sup> reported the case of a 55-year-old man with RA and interstitial pneumonia who deteriorated early after the administration of abatacept. This patient had a rapid clinical and radiographic deterioration of ILD that improved after abatacept was stopped. Nevertheless, other causes of ILD besides the abatacept should be considered, and additional information is required before establishing definite conclusions about the safety of abatacept in patients with RA-ILD.

### Lung transplantation and RA-ILD

Several studies have demonstrated that patients with

systemic sclerosis had similar rates of survival after lung transplantation compared with patients who had idiopathic pulmonary fibrosis or idiopathic pulmonary arterial hypertension<sup>[143]</sup>. Nevertheless, there are only few studies evaluating outcomes in patients with RA-ILD who underwent lung transplantation. Yazdani *et al.*<sup>[144]</sup> performed a retrospective study to examine survival in 10 patients with RA-ILD who received a lung transplant, compared with 53 patients with IPF and 17 with systemic sclerosis-ILD (SSc-ILD). The authors reported similar cumulative survival rates in RA-ILD compared to IPF (67% vs 69%, respectively), although the cumulative survival rate was higher in SSc-ILD (82%). These data suggest that RA-ILD patients have a similar cumulative survival rate compared to other recipient of lung transplant, and therefore lung transplant should be considered in patients with refractory ILD who have not responded to other therapeutic strategies.

### Other treatments

Some treatments used for idiopathic pulmonary fibrosis have been infrequently investigated in patients with rheumatic disorders associated ILD. These treatments include (1) pirfenidone; (2) bosentan and sildenafil; (3) imatinib; and (4) warfarin. Pirfenidone is an antifibrotic drug that inhibits fibroblast proliferation and collagen synthesis and clinically is used for IPF. In an open-label trial, Nagai *et al.*<sup>[145]</sup> evaluated the effects of one year of treatment with oral pirfenidone (40 mg/kg body weight) in patients with advanced pulmonary fibrosis secondary to systemic sclerosis without observing a survival benefit, although these patients had no significant deterioration in chest radiographic findings or arterial oxygen pressure. To date, there have been no studies evaluating pirfenidone in RA-ILD. Therefore, new evidence derived from such studies is required. Bosentan is an endothelin-1 antagonist used in patients with pulmonary arterial hypertension. However, most of the information of bosentan's effects on CTD-ILD is derived from patients with systemic sclerosis. Mittoo *et al.*<sup>[146]</sup> performed a retrospective assessment of 13 patients with CTD-ILD and pulmonary hypertension. Only 2/13 of these patients had RA-ILD. These patients received bosentan alone, sildenafil alone or bosentan plus sildenafil. This study found that the drugs used to treat pulmonary hypertension were well tolerated, with higher mortality rates among patients with systemic sclerosis compared with other CTD. New studies evaluating bosentan in RA-ILD are required to draw definite conclusions. Imatinib mesylate inhibits the activation of the PDGF receptor, as well as the c-Abl, Bcr-Abl and c-Kit tyrosine kinases. Consequently, imatinib mesylate suppresses the activation and proliferation of fibroblasts, requiring this drug to be evaluated in RA-ILD<sup>[147]</sup>. Warfarin has been only evaluated in retrospective studies. Watanabe *et al.*<sup>[148]</sup> performed a retrospective analysis of 20 patients with

rapidly progressive interstitial pneumonia, 11 cases of which were secondary to CTD (2/11 were due to rheumatoid arthritis). These authors classified the patients into 2 groups: group A, which included 11 patients treated with anticoagulant therapy (warfarin or dalteparin), and group B, which included 9 patients who did not receive anticoagulation. At the end of the study, patients treated with anticoagulation had a better survival rate compared with the non-anticoagulated group ( $P = 0.038$ ). Nevertheless, this evidence is too weak to recommend the use of warfarin in patients with RA-ILD. N-acetylcysteine is an antioxidant, acts as a scavenger for free radicals and has anti-inflammatory properties. This agent also suppresses the production of TNF- $\alpha$  and TGF- $\beta$  by alveolar macrophages in patients with idiopathic pulmonary fibrosis<sup>[149]</sup>. N-acetylcysteine is an interesting drug in idiopathic pulmonary fibrosis, where it is widely used as an adjuvant therapy, although recent data did not demonstrate significant differences between N-acetylcysteine vs placebo in terms of FVC, frequency of exacerbations or mortality rates<sup>[150]</sup>. To date, limited information exists about the effects of N-acetylcysteine in CTD-ILD. Rosato *et al.*<sup>[151]</sup> evaluated, in a retrospective study, the effects of intravenous N-acetylcysteine in patients with systemic sclerosis, observing a decrease in the rate of deterioration of DLCO, VC and TLC. Nevertheless, to date, no studies have reported the effects of N-acetylcysteine in RA-ILD. Evidence against the use of this drug has appeared in one study that demonstrated an increased risk of death and hospitalization in patients with idiopathic pulmonary fibrosis who received a combination of prednisone, azathioprine and N-acetylcysteine compared with patients who received placebo.

### PROGNOSIS

Predictors of mortality include older age, male sex, lower socioeconomic status, decreased lung function, the presence of fibrosis, the extent of disease, the presence of a lung-injury pattern of usual interstitial pneumonia, higher disease activity scores, higher erythrocyte sedimentation rates, higher lactate dehydrogenase levels, greater baseline pain, and worse health assessment questionnaire scores<sup>[152]</sup>. Average survival in patients with RA is 10-11 years shorter than that of the general population. Lung disease is especially common in RA and is directly responsible for 10%-20% of all RA-associated mortality<sup>[153]</sup>. A retrospective study by Kelly *et al.*<sup>[30]</sup> demonstrated that mortality rates were related to the subtype of lung disease; patients with a UIP/OS pattern had an RR of death from any cause of 3.9 compared with patients who had a pattern of NSIP/cryptogenic organizing pneumonia (COP). These authors observed during follow-up that, compared with limited disease, extensive disease was associated with an RR of death from any cause of 2.17.



Gochuico *et al*<sup>[23]</sup> examined the differences between progressive RA-ILD and stable RA-ILD. Higher alveolar concentrations of IFN- $\gamma$  and TGF- $\beta$ 2 were observed in patients with progressive RA-ILD versus stable RA-ILD. Additionally, patients with progressive RA-ILD were more likely to be treated with MTX, suggesting that treatment with this agent may constitute a risk factor for progression of preclinical RA-ILD. Assayag *et al*<sup>[152]</sup> performed a systematic review evaluating predictors of mortality in RA-ILD. Factors associated with higher mortality rates were older age, male gender, lower DLCO, extent of fibrosis and UIP pattern. Nevertheless, the authors recognized that the review was limited by the low quality of some of the included studies; therefore, larger, well-designed, multicenter studies evaluating prognostic factors in RA-ILD are still required.

## CONCLUSION

Recent evidence indicates that ILD is presently observed more frequently in RA than was the case a decade ago. Establishing an early diagnosis of this complication depends on the level of clinical suspicion, as well as the strategy used to assess patients at risk of ILD. The adequate assessment of patients with suspected ILD should be based on a combination of tests, including clinical assessments, PFT, HRCT, and in some cases BAL or lung biopsy. Currently, distinct clinical subtypes of RA-ILD are recognized that may differ importantly in terms of prognosis and therapeutic response. Efforts to identify the subtype of RA-ILD should be made in order to design a therapeutic strategy that will be of the greatest benefit to a particular patient. In terms of treatment, recently identified therapeutic targets have produced new drugs for evaluation. Nevertheless, most of the information about these treatments is derived from observational or uncontrolled open studies. Therefore, evidence about the effectiveness of these agents is too weak to establish definite conclusions in patients with RA-ILD. New well-designed, randomized, multicenter, double-blinded clinical trials are needed to evaluate the use of novel therapeutic agents in RA-ILD. This represents an important opportunity for future research.

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