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REVIEW

The Lung in Rheumatoid Arthritis

Focus on Interstitial Lung Disease

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Interstitial lung disease (ILD) is an increasingly recognized complication of rheumatoid arthritis (RA) and is associated with significant morbidity and mortality. In addition, approximately one-third of patients have subclinical disease with varying degrees of functional impairment. Although risk factors for RA-related ILD are well established (e.g., older age, male sex, ever smoking, and seropositivity for rheumatoid factor and anti–cyclic citrullinated peptide), little is known about optimal disease assessment, treatment, and monitoring, particularly in patients with progressive disease. Patients with RA-related ILD are also at high risk of infection and drug toxicity, which, along with comorbidities, complicates further treatment decision-making. There are distinct histopathologic patterns of RA-related ILD with different clinical phenotypes, natural histories, and prognoses. Of these, the usual interstitial pneumonia (UIP) subtype of RA-related ILD shares a number of clinical and histopathologic features with idiopathic pulmonary fibrosis, the most common and severe of the idiopathic interstitial pneumonias, suggesting the existence of common mechanistic pathways and possibly therapeutic targets. There remain substantial gaps in our knowledge of RA-related ILD. Concerted multinational efforts by expert centers has the potential to elucidate the basic mechanisms underlying RA-related UIP and other subtypes of RA-related ILD and facilitate the development of more efficacious and safer drugs.

Introduction

Pulmonary involvement is a common extraarticular manifestation of rheumatoid arthritis (RA) and occurs, to some extent, in 60–80% of patients with RA (1,2). The pulmonary disease associated with RA can affect any of the lung compartments and can be either secondary to the underlying RA or a complication of RA therapy, such as opportunistic infection and drug toxicity. One particular type of pulmonary involvement in RA is interstitial lung disease (ILD), which is associated with significant morbidity and mortality (3–5) and is the focus of this review.

Epidemiology and risk factors

The precise prevalence and incidence of RA-related ILD are unknown but range from 1% to 58% depending on the methodology used (1,4,6–10). Population-based studies in the US suggest that the cumulative incidence of clinically significant RA-related ILD (defined as abnormal high-resolution computed tomography [HRCT] and lung function tests with clinical manifestations of ILD) is 5% at 10 years (11), 6.3% at 15 years (12), and 6.8% over 30 years of follow-up (1). Another study that reviewed US death certificates in decedents with RA identified clinically significant ILD in 6.8% of women and 9.8% of men (4). However, studies that rely on medical records review and medical coding are subject to reporting bias and generally

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include only patients with clinically significant disease. Another factor that complicates determining the prevalence and incidence of RA-related ILD is that the ILD is often underrecognized (13). Patients with RA who undergo screening, regardless of the presence of symptoms, often have radiologic abnormalities on HRCT, referred to as subclinical ILD and/or interstitial lung abnormalities. The prevalence of subclinical ILD is variable and ranges from 19% to 57% (10,14). These radiographic findings are reported to be progressive in ~50% of cases (6) and are associated with increased respiratory symptoms and impaired lung function (15). Nonetheless, tools are lacking to predict the individual risk of progression to clinically significant RA-related ILD.

There are several recognized risk factors for the development of ILD in patients with RA. The most consistently reproduced associations across studies include older age (3,12,16), male sex (3,10,14), a history of ever smoking (6,14,17), and seropositivity for rheumatoid factor (RF) or anti–cyclic citrullinated peptide (anti-CCP) antibodies (6,13,17). Interestingly, smoking is associated with both an increased risk of RA (18) and a greater risk of developing RA-related ILD (13,18). RA disease activity has also been associated with the development of RA-related ILD, although these associations are less clear (3,12).

Hypothetical mechanisms behind the concomitance of joint and lung involvement

The mechanisms of ILD in RA are poorly understood, but genetic and environmental factors are believed to play a role (19,20). HLA–B54, HLA–DQ1B*0601, HLA–B40, and the site encoding α-1 protease inhibitor are associated with an increased risk of ILD in patients with RA (19). In addition, a conserved amino acid sequence at position 70–74 (QKRAA, RRRAA, or QRRAA) in the HLA–DRβ chain, referred to as the shared epitope (SE), is shared between the RA-associated HLA–DR alleles (21–23). Notably, the SE confers susceptibility to the development of RA and is highly associated with the presence of anti-CCP antibodies. Citrullination is the posttranslational enzymatic conversion of arginine to citrulline. In patients who also possess the SE, citrullinated residues may act as neoepitopes that break immunologic tolerance and become a target for autoimmunity (24,25). The site where this initial event occurs is unknown, but evidence points toward mucosal sites (26).

Two potential pathways linking joint and lung involvement have been proposed (27). In one of the pathways, RA-related ILD would begin in the synovial tissue following an immune response against citrullinated proteins that subsequently cross-react with similar antigens in the lung. The plausibility of this hypothesis stems from the observation that the majority of patients with RA-related ILD develop articular disease prior to lung involvement. In such cases, lung histology would exhibit an inflammatory non–usual interstitial pneumonia (non-UIP) pattern of disease. In the second pathogenetic paradigm, immune tolerance breakdown takes place in the lung, and ILD (including UIP) triggers an immune response against citrullinated proteins that secondarily spreads to the joints. The observations that ILD might precede extrapulmonary manifestations of RA by years (6,10), that an increased number of citrullinated peptides may be seen in the lung parenchyma of patients with RA-related ILD, and that the lung might locally produce RA-related autoimmunity lend support to this latter hypothesis (28,29).

Smoking is believed to play a major role in the pathogenesis of RA-related ILD. Lung injury from cigarette smoking and other sources of oxidative stress may contribute to citrullination of proteins and the creation of new epitopes that trigger SE-restricted autoimmune responses characterized by cellular infiltration and release of profibrotic cytokines (e.g., interleukin-4 [IL-4], IL-13, and transforming growth factor β [TGFβ]), chemokines, and growth factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) that promote fibroblast proliferation and differentiation to myofibroblasts. However, smoking may also induce the activation of profibrotic pathways through repetitive injury to the alveolar epithelium. In turn, matrix metalloproteinases released from damaged epithelia may promote further cellular recruitment and activation of cytokines and profibrotic mediators, thereby amplifying the cross-talk between inflammatory and tissue-remodeling pathways.

Clinical features

The clinical manifestations of RA-related ILD resemble those of idiopathic interstitial pneumonias, although, in contrast to patients with idiopathic interstitial pneumonias, patients with RA-related ILD may remain asymptomatic despite significant radiographic abnormalities. The most common presenting symptoms include exertional dyspnea, which, in patients with debilitating arthritis pain may be masked by limited mobility and nonproductive cough. Physical signs of respiratory involvement may be minimal or absent despite the presence of radiographic abnormalities, but tachypnea and bibasilar inspiratory crackles are common (30). Pleural rubs may also be heard, and, in advanced disease, cyanosis, edema, and signs of pulmonary hypertension (PH) may occur. As with other connective tissue diseases (CTDs), in RA patients, PH

should be suspected in the presence of symptoms or exercise-induced arterial oxygen desaturation disproportionate to the severity of lung involvement. Clubbing has been reported in as many as 75% of patients with RA-associated UIP but occurs significantly less frequently in those with other patterns of RA-related ILD (31). The temporal relationship between articular disease and ILD is variable. One study showed a median duration of 4.9 years from the diagnosis of RA to the diagnosis of ILD (32), but lung disease may also precede the joint manifestations (33). The severity and extent of lung involvement do not necessarily correlate with the severity of RA, although high titers of RF are a known risk factor for the development of ILD.

Disease phenotypes

There are well-recognized phenotypes among patients with RA-related ILD. One of the more notable distinctions that often is made is the relationship to the UIP pattern of disease. Indeed, in contrast to patients with other CTD-related ILDs (e.g., systemic sclerosis [SSc], idiopathic inflammatory myositis, and mixed connective tissue disease), in which a nonspecific interstitial pneumonia (NSIP) pattern is most frequently seen, patients with RA have the highest prevalence of a UIP pattern (34), both pathologically and radiologically (Table 1). Patients with RA-related ILD with a histologic UIP pattern tend to be older, more frequently are male, and more frequently are active or former smokers compared with patients with RA-related ILD with a non-UIP pattern (5,6,32,33). Other data suggest that patients with RA-related ILD with a UIP pattern experience more respiratory system–related hospitalizations (35) and worse survival compared with those with a non-UIP pattern, although some of the data are mixed (5,36,37).

Similar to idiopathic UIP (e.g., idiopathic pulmonary fibrosis [IPF]), the clinical course of RA-related UIP is highly variable and can be punctuated by episodes of acute decompensation termed "acute exacerbations." In IPF, acute exacerbation is defined as a clinically significant worsening (or development) of dyspnea and lung function typically of <1 month duration, accompanied by new widespread pulmonary infiltrates on chest radiography or HRCT in the absence of cardiac failure and fluid overload (38). There are no studies comparing the prevalence of acute exacerbation across the spectrum of CTD-related ILD, but patients with a UIP pattern appear to be at higher risk for this complication irrespective of the underlying disease (39). In a retrospective study of 51 patients with RA-related ILD, acute exacerbation occurred in as many as 22% (11 of 51 patients) during a median follow-up period of 8.5 years, with a mortality rate of 64% (7 of 11 patients) (40). As expected, patients who experienced acute exacerbation had significantly worse survival compared with those who did not have acute exacerbation ($P = 0.001$). The overall 1-year incidence of acute exacerbation was 2.8% (6.5% in the UIP group and 1.7% in the non-UIP group). Older age at diagnosis, UIP pattern on HRCT, and methotrexate (MTX) treatment were associated with the development of acute exacerbation on univariate analysis, whereas the study was too small to perform multivariate analysis (40).

Given the phenotype of UIP in RA-related ILD, comparisons with IPF have been made. Patients with RA-related ILD with a UIP pattern on HRCT have similar age, sex distribution, and smoking history compared with patients with IPF (5,27). The radiologic pattern of UIP in RA-related ILD is also predictive of UIP on surgical lung biopsy, similar to what has been demonstrated in IPF (41). Finally, clinical predictors of mortality appear to be similar between RA-related UIP and IPF (40). NSIP occurs in approximately one-third of patients with RA-related ILD (33) and is generally associated with a longer duration of articular manifestations, a lower risk of disease progression, a better response to treatment, and better overall outcomes compared with UIP (5,6,36,42). The most common presenting symptoms are dyspnea and cough that have developed over weeks to months. Occasionally, patients initially diagnosed as having idiopathic NSIP may develop RA over time (43). The clinical course of RA-related NSIP is heterogeneous, with some patients remaining relatively stable and others (a minority) experiencing rapid deterioration (40). In addition, less frequent patterns of RA-related ILD include organizing pneumonia, lymphocytic interstitial pneumonia, diffuse alveolar damage, and desquamative interstitial pneumonia.

Imaging

Radiographic surveys for the presence of ILD are insensitive and imprecise in patients with RA. In a prospective study of asymptomatic patients with early disease, chest radiograph showed features of ILD in 6% of patients, and HRCT showed such features in 33% of patients (10). Abnormal chest radiographs can show bibasilar ground-glass opacities, reticular and nodular changes, and honeycombing. In advanced disease, enlargement of central pulmonary arteries and attenuation of peripheral vessels may suggest PH. On HRCT, ILD abnormalities are more extensive in males, patients with severe deforming joint disease, and those with high RF titers (9,10). However, in a study of 84 patients with longstanding RA, HRCT abnormalities were present in as many as 11 of 38

Table 1. Clinical, radiologic, and pathologic features across the spectrum of connective tissue disease–associated interstitial lung disease*

Disease	Epidemiology	Clinical manifestations	HRCT	Histologic findings
RA	Most cases occur at age 50–60 years. Male sex, longstanding disease, high RF titers, and history of cigarette smoking increase the risk of ILD.	Dyspnea at rest or with exertion and dry cough.	Bibasilar reticulation with or without honeycombing, ground-glass opacity, centrilobular branching lines with or without airway dilatation and consolidation.	UIP (predominantly), NSIP, LIP, OP.
SSc	The prevalence of ILD is significantly higher in patients with more extensive skin involvement and ranges from 10% to 50%. Anti-topo antibodies are a risk factor for the development of ILD, while ACAs are protective.	Fatigue, dyspnea and cough, either dry or productive.	Ground-glass attenuation, irregular linear opacities, small nodules, traction bronchiectasis, bilateral pleural thickening, honeycombing. Centrilobular nodules and fibrosis suggest recurrent aspiration.	NSIP (predominantly) and UIP. RB-ILD and OP are rare.
SS	More common in patients with more severe and extraglandular manifestations.	Exertional dyspnea and dry cough.	Ground-glass attenuation, centrilobular and subpleural nodules, linear opacities, interlobular septal thickening, bronchial wall thickening, bronchiectasis, and thin-walled cysts. Honeycombing is rare.	NSIP, OP, LIP, UIP, amyloidosis, constrictive bronchiolitis.
SLE	Uncommon (<5% of cases). Mean age at presentation is ~50 years.	Dry cough, dyspnea, pleuritic chest pain.	Intralobular and interlobular septal thickening, traction bronchiectasis, ground-glass opacity, consolidation. Honeycombing is rare.	NSIP (predominantly), UIP, LIP, OP, DAD in acute lupus pneumonitis. DAH, chronic thromboembolic disease and vasculitis can also be seen.
PM/DM	Prevalence of ILD 30–80% and higher in DM. Presence of an antisynthetase antibody is highly predictive of the development of ILD.	Acute/subacute onset of cough and dyspnea frequently accompanied by fever in acute ILD (more common in DM). Progressive dyspnea on exertion and dry cough in chronic ILD.	Bilateral lower-lobe irregular linear opacities, consolidation, ground-glass opacity, micronodules. Honeycombing is rare.	NSIP (predominantly), OP, UIP, DAD.
MCTD	ILD occurs in ~50–66% of patients.	Dry cough, dyspnea, and pleuritic chest pain.	Ground-glass attenuation and linear opacities with a peripheral and lower lobe predominance.	All histologic features of PM/DM, SLE, or SSc can be found.
AS	Rare (<5%). Male preponderance (M:F ratio 50:1).	Often asymptomatic. Cough, sputum, and dyspnea.	Apical fibrosis (usually bilateral), interlobular septal thickening, pleural thickening, parenchymal bands.	Early changes consist of a patchy pneumonic process. In advanced cases, dense pleural and pulmonary fibrosis (with or without bronchiectasis) predominates.

* HRCT = high-resolution computed tomography; RA = rheumatoid arthritis; RF = rheumatoid factor; UIP = usual interstitial pneumonia; LIP = lymphycytic interstitial pheumonia; OP = organizing pneumonia; SSc = systemic sclerosis; anti-topo = antitopoisomerase; ACAs = anticentromere antibodies; NSIP = nonspecific interstitial pneumonia; RB-ILD = respiratory bronchiolitis–associated interstitial lung disease; SS = Sjögren's syndrome; SLE = systemic lupus erythematosus; DAD = diffuse alveolar damage; DAH = diffuse alveolar hemorrhage; PM/DM = polymyositis/dermatomyositis; MCTD = mixed connective tissue disease; AS = ankylosing spondylitis.

(29%) asymptomatic patients and 27 of 39 (69%) symptomatic patients (44).

The spectrum of parenchymal changes that can be observed include ground-glass opacity, bronchiectasis/bronchiolectasis, linear opacities, and honeycombing (Figures 1A and B). Reticular changes, traction bronchiectasis/bronchiolectasis, and honeycombing are consistent with UIP; extensive ground-glass attenuation suggests NSIP, acute interstitial pneumonia, or desquamative interstitial pneumonia; and areas of subpleural consolidation suggest organizing pneumonia. In a large study of patients with RA-related lung disease, 4 major HRCT patterns of disease were identified, namely UIP (37%), NSIP (30%), obliterative bronchiolitis (17%), and organizing pneumonia (8%). Notably, in patients who underwent lung biopsy, the CT findings correlated with the pathologic findings in the majority of cases (45). A recent study showed that in patients with RA-related ILD, a *definite* UIP pattern on HRCT (characterized by basal, subpleural reticular opacities, traction bronchiectasis, and honeycombing) has a specificity of 96% and a sensitivity of 45% for histopathologic UIP, indicating that radiologic RA-related UIP may display features that mimic other patterns of disease (e.g., NSIP) (41). This point is not trivial, because patients with RA-related ILD rarely undergo surgical lung biopsy.

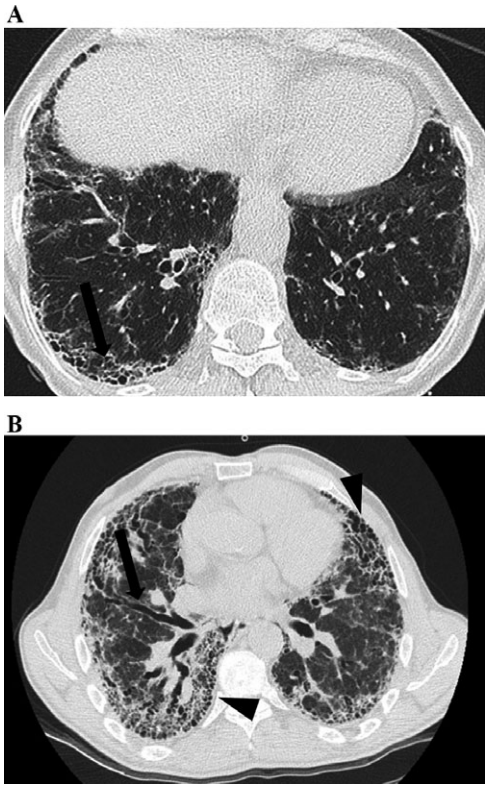

Figure 1. A, Interstitial lung disease in a 57-year-old man with rheumatoid arthritis (RA). Subpleural reticular opacities, cystic changes (**arrow**), and traction bronchiectasis in the lower lobes are shown. **B,** Advanced pulmonary fibrosis in a 62-year-old man with RA who was listed for lung transplantation. Bilateral predominantly subpleural reticular changes, traction bronchiectasis (**arrow**), and honeycombing (**arrowheads**) consistent with the usual interstitial pneumonia pattern are shown.

Diffuse ground-glass opacity on CT may be difficult to differentiate from desquamative interstitial pneumonia, particularly in smokers with RA. However, the diagnosis of desquamative interstitial pneumonia requires histologic confirmation. Conversely, features of desquamative interstitial pneumonia often overlap with those of NSIP and UIP in patients with RA-related ILD. Similarly, although lymphocytic interstitial pneumonia may be present in histologic specimens from RA patients, its distinguishing CT features (ground-glass opacity and/or reticular changes with lung cysts) are uncommon in patients with RA-related ILD and are far less frequent than in patients with primary Sjögren's syndrome.

Several non-ILD pulmonary features can be seen on imaging that are important to consider when evaluating patients with new-onset or established RA-related ILD. Airway involvement encompasses a number of abnormalities, including follicular bronchiolitis, bronchiectasis, and obliterative bronchiolitis. Follicular bronchiolitis is characterized on HRCT by centrilobular nodules measuring 1–12 mm in diameter, variably associated with peribronchial nodules and patchy areas of ground-glass opacity, while the CT appearance of obliterative bronchiolitis typically consists of a mosaic attenuation pattern with areas of air trapping on expiratory CT scan. Mild bronchial dilatation and wall thickening are common accompanying features. Rheumatoid nodules are generally associated with the presence of subcutaneous nodules and may wax and wane. Rheumatoid nodules may be single or multiple, of varying size (from a few millimeters to several centimeters), well circumscribed, and with the tendency to cavitate. Subpleural rheumatoid nodules may cause bronchopleural fistula or pneumothorax. Rheumatoid nodules should be closely monitored clinically and radiologically, because differentiating them from pulmonary neoplasm (e.g., carcinoma or lymphoma) or amyloidosis may be challenging.

Pulmonary function tests

In patients with RA-related ILD, pulmonary function tests may reveal a restrictive ventilatory defect with decreased diffusing capacity of the lung for carbon monoxide (DLCO) even in the absence of symptoms. In a study of patients with early RA, 33% had a DLCO of <80% of that predicted, while only 14% had symptoms (10). The DLCO is highly sensitive for predicting the

presence of ILD, whereas lung volumes may be more useful than DLCO for assessing disease extent (46,47). Similar to IPF, changes over time that are considered clinically relevant include a decrease in forced vital capacity (FVC) of ≥10% or a decrease in the DLCO of ≥15% over 6–12 months (47).

Bronchoalveolar lavage (BAL)

Findings in BAL fluid obtained from patients with RA-related ILD are frequently abnormal but are nonspecific, although an increase in the neutrophil count is more common in patients with UIP, and a lymphocytic cytology is more frequent in patients with NSIP or organizing pneumonia. In addition, BAL lymphocytosis is more common in RA patients without ILD (48). However, abnormalities in the cellular constituents of BAL fluid are not useful for predicting outcome or response to treatment. As a result, BAL is not routinely performed in the diagnostic work-up of patients with RA-related ILD. In RA patients with an acute onset or worsening of respiratory symptoms and radiographic abnormalities, BAL is useful for excluding ILDs other than RA-related ILD, malignancy, or infection (47).

Pathology

RA may be associated with a variety of pleural and pulmonary pathologies, including ILD, pleuritis, bronchiolitis, vascular abnormalities, and rheumatoid nodules (49,50). However, with the exception of rheumatoid nodules, very few of the histologic lesions observed in patients with RA are unique, while the majority of them display features that overlap with those of other entities (e.g., UIP/IPF).

In autopsy studies, pleural involvement has been reported in up to 70% of RA patients (51); however, most cases are asymptomatic and of no clinical relevance (52). Typically, pleural effusion has features of a sterile exudate with low pH (<7.3), a low glucose level (<60 mg/dl), and an elevated lactate dehydrogenase level (>700 IU/liter) (53). Chronic pleuritis is characterized by thickening of the visceral pleura by fibrous connective tissue and a chronic infiltration of lymphocytes and plasma cells. In the early phases of rheumatoid pleuritis, fibrin deposition with neutrophilic exudate is a common finding (49,54), while late phases are characterized by chronic inflammatory infiltrates accompanied by mesothelial hyperplasia with fibroblasts and elongated histiocytes perpendicularly oriented to the pleural surface (49,54). Cellular interstitial pneumonia with aggregates of lymphoid tissue (Figure 2) and follicular bronchitis/bronchiolitis, which consists of peribronchial/peribronchiolar lymphoid follicles with secondary germinal centers, are additional common findings (30,55,56).

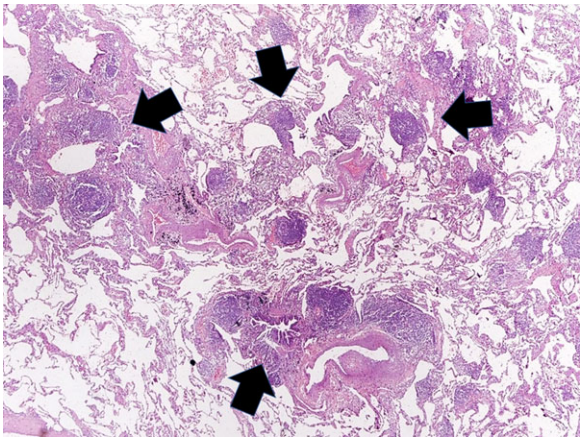

Figure 2. Photomicrograph showing highly cellulated interstitial pneumonia with several aggregates of nodular lymphoid tissue (**arrows**) around bronchi and bronchioles in a patient with rheumatoid arthritis. Hematoxylin and eosin stained; original magnification × 40.

RA may be complicated by a spectrum of ILD patterns, and UIP is more prevalent than NSIP (33,34,55,57) (Figure 3). A UIP pattern, which is characterized by patchy heterogeneous fibrosis with honeycomb changes, and actively fibrogenic "fibroblastic foci" (56) can be seen in 28–61% of patients with RA-related ILD (41,58). Compared with IPF, RA-related UIP is characterized by the concurrent presence of chronic pleuritis, follicular bronchiolitis, or cellular bronchiolitis with interstitial chronic infiltrates. In addition, lung biopsy specimens obtained from patients with RA-related UIP have an increased number of CD4+ lymphocytes compared with those from IPF patients (59).

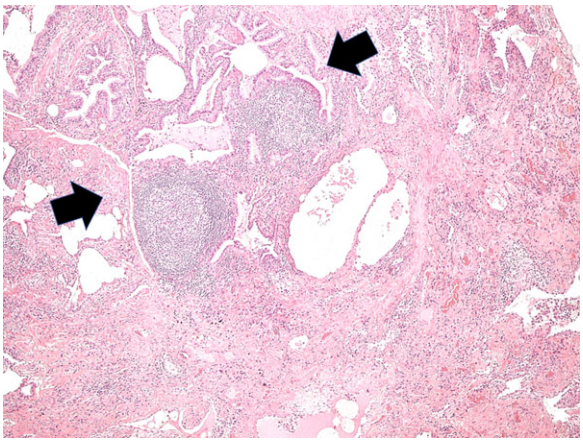

Figure 3. Photomicrograph showing interstitial lung disease with a usual interstitial pneumonia pattern and scattered follicular bronchiolitis (**arrows**) secondary to rheumatoid arthritis. Hematoxylin and eosin stained; original magnification × 100.

Surgical lung biopsy is generally not required in patients with RA-related ILD, unless the diagnosis of CTD is unclear or not established (e.g., when ILD precedes the onset of articular manifestations of RA). Bronchiolar chronic inflammatory infiltrates, interlobular lymphoid hyperplasia, cellular interstitial pneumonia, desquamative interstitial pneumonia, and bronchiolitis obliterans with organizing pneumonia, which may lead to constrictive bronchiolitis, are additional histologic manifestations of RA-related ILD. Lung abnormalities in RA patients may also be secondary to drug toxicity (e.g., MTX) or superimposed opportunistic infections. Therefore, pathologists should be familiar with drug-induced lung injury in patients with RA who are receiving immunosuppressive therapy, because virtually all drugs used to treat RA can cause lung toxicity with patterns identical to those observed in RA-related ILD, such as cellular NSIP with or without granulomas (MTX), organizing pneumonia and cellular interstitial pneumonia (rituximab), and diffuse alveolar damage (leflunomide) (www.pneumotox.com) (Table 2). A small proportion of patients with RA have rheumatoid nodules (54,57), which may be single or multiple and are typically located in the interlobular septa or on the pleural surface. The occurrence of potentially life-threatening infections should also be considered in patients with RA-related ILD. In suspected cases, special stains (e.g., methenamine–silver, periodic acid–Schiff, and Ziehl-Neelsen) should be performed when examining BAL fluid or lung tissue.

Management

The optimal treatment of RA-related ILD has not been determined and is largely based on data derived from other CTD-related ILDs, primarily SSc-associated ILD. Therefore, careful attention should be paid to the baseline assessment of disease severity, presentation (acute, subacute, and chronic), and the risks and benefits of therapy for each patient. In general, treatment should be considered in patients with clinical, functional, or radiologic deterioration and histopathologic patterns other than UIP (e.g., NSIP, organizing pneumonia, and lymphocytic interstitial pneumonia). However, in a retrospective study of 84 patients with RA-related UIP, 29 of whom were treated due to poor lung function or ILD progression, glucocorticoids alone or in combination with immunosuppressive agents improved or stabilized the disease in 50% of the patients (37). In IPF, however, the combination of glucocorticoids and immunosuppressive therapy is contraindicated (60).

Table 2. Potential noninfective pulmonary complications associated with drugs used to treat RA*

Complication	Drug
Fibrosis	Azathioprine, cyclophosphamide, gold, methotrexate, sulfasalazine
Obliterative bronchiolitis	Gold, sulfasalazine
Drug-induced lupus	Sulfasalazine, TNF inhibitors
Noncardiogenic pulmonary edema	Aspirin (high-dose), colchicine (overdose), cyclophosphamide, methotrexate, NSAIDs, rituximab, tocilizumab
Pneumonia	Anakinra, azathioprine, cyclophosphamide, gold, leflunomide, methotrexate, NSAIDs, rituximab, sulfasalazine, TNF inhibitors, tocilizumab

* RA = rheumatoid arthritis; TNF = tumor necrosis factor; NSAIDs = nonsteroidal antiinflammatory drugs.

Glucocorticoids are the mainstay of clinical management, and therapy is generally initiated with oral prednisone at a daily dose of 0.5 mg/kg, with gradual tapering over weeks to months based on the clinical response (47). An immunosuppressive agent such as mycophenolate mofetil (MMF) or azathioprine may be added to treatment in patients who fail to respond to or experience intolerable side effects of glucocorticoid treatment, although MTX is generally avoided in patients with RA-related ILD due to the risk of lung toxicity (see below). The safety and efficacy of MMF have been examined in a large cohort of patients with CTD-associated ILD (n = 125), including 18 patients with RA-related ILD (61), treated with MMF for a median of 897 days. Overall, the drug was well tolerated, with a discontinuation rate due to adverse events of less than 10%. In addition, MMF treatment was associated with improvement in the FVC and the DL_{CO} in the subgroup of patients without UIP and with stability of these same parameters in patients with UIP. Among patients with RA-related ILD, the FVC trended downward prior to MMF initiation and upward following MMF treatment. In a large observational study of rituximab-treated patients with RA (n = 700), including 56 patients with RA-related ILD, most patients remained stable or improved after treatment over a prolonged follow-up period (62). Notably, patients who deteriorated or died had the most severe ILD prior to rituximab initiation.

In severe and progressive forms of RA-related ILD, lung transplantation is a reasonable option, although extrapulmonary disease manifestations may complicate transplantation, while side effects of long-term treatment of RA (e.g., osteoporosis) may be a contraindication. However, in a retrospective review of patients with RA-related ILD (n = 10) who underwent lung transplantation, 1-year survival was comparable with that in lung transplant recipients with IPF (67% and 69%, respectively)

(63). Another study with a broader population of patients with non-SSc CTD-related lung disease, including RA, demonstrated similar findings (64).

Pulmonary toxicity of drugs used to treat RA. Several drugs used to treat RA may induce lung toxicity (Table 2). MTX, one of the most effective and commonly used agents for the treatment of articular manifestations of RA, is one such drug. A meta-analysis of randomized controlled trials demonstrated an increased risk of pulmonary complications in RA patients treated with MTX (65). Another study suggested that MTX may be a risk factor for progression of preclinical ILD (6). However, in a large prospective study of patients starting low-dose MTX treatment (n = 223, 154 of whom had RA) only ~1% developed pneumonitis, suggesting that this complication is not as common as previously thought (66). Similarly, a systematic literature search including 21 prospective studies of MTX monotherapy identified only 15 cases of pneumonitis among 3,463 patients receiving low-dose MTX (0.43%) for up to 36.5 months (67). Conversely, MTX treatment is associated with an increased risk of developing pulmonary toxicity in patients with preexisting ILD and should be avoided in this setting (68,69). Controversy also exists for tumor necrosis factor inhibitors (TNFi) and rituximab, with some studies showing improvement and others demonstrating worsening or development of ILD (70,71). However, recent reviews and meta-analyses suggest that serious respiratory adverse events in patients receiving TNFi have probably been overestimated (72). The risks and benefits of these drugs must be weighed carefully, but in patients with extensive or progressive pulmonary disease, the potential benefits often outweigh the risks of drug toxicity (30).

RA-related ILD and risk of infection. Patients with RA-related ILD are at increased risk of serious infections due to a combination of lung disease, immunosuppressive treatment, and abnormality of the immune system. This concern has been confirmed by a recent meta-analysis showing that the risk of infection increases with an increasing immunosuppressant burden (73). In addition, in a large cohort of patients with RA-related ILD, the risk of serious infections (i.e., those requiring antibiotic treatment or hospitalization) was higher in those receiving daily prednisone doses of >10 mg during the first year after ILD diagnosis and in patients with an organizing pneumonia pattern (compared with UIP and NSIP) (74). Fifty-four serious infections were identified (for an infection rate of 7.4 per 100 person-years), with pneumonia, septicemia, and opportunistic infections representing the most common types of infection. Notably, 15 of 72 deaths (21%) were directly attributable to infection.

Prognosis

ILD is second only to cardiac disease as a cause of mortality in patients with RA (3,4,30). In a large UK inception cohort of patients with RA, pulmonary fibrosis was the primary cause of death in 3.9% of cases (18 of 459) and contributed to or was a comorbid condition in another 17 deaths (17 of 459 [3.7%]) (75). In addition, ILD-associated PH may contribute to the high incidence of cardiovascular disease–related deaths in patients with RA. Indeed, although cases of isolated PH have also been described, particularly in older patients and those with a longer disease duration (76), PH generally occurs in the context of RA-related ILD.

Several predictors of mortality have been identified in RA-related ILD (5,17,34,77–79). Major limitations to these prior studies, however, have been the methodology and sample size. Age is the most consistent variable that has been identified as a significant predictor of a poor prognosis across multiple studies. Other variables associated with RA-related ILD mortality include male sex, disease severity as assessed by the DLco and FVC, the extent of fibrosis on HRCT, a UIP pattern, acute exacerbation, and RA disease activity (5,12,56,77–82). More

Table 3. Ongoing clinical trials of pharmacologic interventions in RA-related ILD*

Trial identifier	Trial characteristics				
	Intervention	Condition	Phase	Primary end point	Status
NCT02808871	Pirfenidone vs. placebo	RA-related ILD	II	Progression-free survival	Not yet recruiting
EudraCT no. 2014-000861-32	Pirfenidone vs. placebo	Progressive non-IPF lung fibrosis†	II	Change in FVC	Recruiting
NCT02999178	Nintedanib vs. placebo	Progressive fibrosing ILD†	III	Annual rate of decline in FVC	Recruiting
NCT03084419	Abatacept	RA-related ILD	II (open-label)	Change in FVC	Not yet recruiting

* RA = rheumatoid arthritis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; FVC = forced vital capacity.
† The study population may include patients with RA-related ILD.

recently, women with seropositive RA have been shown to have a nearly 3-fold increased risk of mortality due to respiratory disease (including chronic obstructive pulmonary disease, asthma, pleurisy, lung abscess, bronchiectasis, and pulmonary fibrosis) compared with women without RA (83).

The potential of IPF-specific antifibrotic drugs in RA-related ILD

RA-related ILD, particularly in patients with a UIP pattern, shares a number of phenotypic features with IPF, suggesting that RA-related ILD and IPF might also overlap biologically and therapeutically (27,31). However, although treatment of RA-related ILD generally consists of anti-inflammatory and/or immunosuppressive agents, in IPF, immunosuppression (e.g., combination therapy with azathioprine, prednisone, and *N*-acetylcysteine) is associated with increased all-cause mortality, hospitalization rate, and serious adverse events (84). Because a large proportion of patients with RA-related ILD have a histologic UIP pattern, it is expected, albeit not demonstrated, that they also may not benefit from immunosuppressive therapy.

Pirfenidone, a compound with antifibrotic, antiinflammatory, and antioxidant properties, and nintedanib, an intracellular inhibitor of multiple tyrosine kinases, including fibroblast growth factor receptor 1, VEGF receptor 2, and PDGF receptor α (PDGFRα) and PDGFRβ, have recently been approved for the treatment of IPF, based on their ability to reduce functional decline and disease progression (85,86). Given the mechanistic similarities between RA-related UIP and IPF, patients with RA-related UIP may potentially benefit from antifibrotic treatment, and a number of studies are currently evaluating the safety, tolerability, and efficacy of antifibrotic drugs in RA-related ILD (Table 3). Despite the plausible rationale of antifibrotic therapy in RA-related ILD, there are no published data for antifibrotic therapy in RA-related ILD. There is also some concern that TGFβ inhibitors, such as pirfenidone and, to a lesser extent, nintedanib, may increase joint inflammation, although joint pain was an uncommon adverse event in clinical trials of pirfenidone in patients with IPF (87).

Conclusions

ILD is a frequent complication of RA and is associated with increased morbidity and mortality. Despite extensive research in this field, there remain substantial gaps in knowledge, particularly with regard to 1) identification, clinical significance, and management of subclinical ILD in patients with RA; 2) assessment, staging, and monitoring of RA-related ILD; 3) identification of patients at higher risk of disease progression and mortality; 4) management of progressive disease; 5) potential utility of antifibrotic therapies in RA-related UIP; and 6) role of mechanisms involved in the pathogenesis of IPF (e.g., alterations in telomere biology and genetics) in RA-related ILD. A collaborative effort by expert centers has the potential to answer some of these questions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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