A Roadmap to Promote Clinical and Translational Research in Rheumatoid Arthritis-Associated Interstitial Lung Disease

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Rheumatoid arthritis (RA) is a systemic inflammatory disorder affecting approximately 1.3 million adults in the United States. Approximately 10% of these individuals with RA have clinically evident interstitial lung disease (RA-ILD), and an additional one-third demonstrate subclinical ILD on chest CT scan. The risk of death for individuals with RA-ILD is three times higher than for patients with RA without ILD, with a median survival after ILD diagnosis of only 2.6 years. Despite the high prevalence and mortality of RA-ILD, little is known about its molecular features and its natural history. At present, we lack a standard validated approach to the definition, diagnosis, risk stratification, and management of RA-ILD. In this perspective, we discuss the importance of clinical and translational research and how ongoing research efforts can address important gaps in our knowledge over the next few years. Furthermore, recommendations are made to design multicenter collaborative studies that will expedite the development of clinical trials designed to decrease the significant morbidity and mortality associated with RA-ILD.

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Abbreviations: ACPA = anticitrullinated protein antibody; CCP = cyclic citrullinated peptide; CTD = connective tissue disease; CXCL = CXC chemokine ligand; DLCO = diffusing capacity of lung for carbon monoxide; DMARD = disease-modifying antirheumatic drug; HRCT = high resolution CT; IIP = idiopathic interstitial pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; KL-6 = Krebs von den Lungen-6; MMP = matrix metalloproteinase; PDGF = platelet-derived growth factor; PFT = pulmonary function test; RA = rheumatoid arthritis; RA-ILD = rheumatoid arthritis-associated interstitial lung disease; RF = rheumatoid factor; SP = surfactant protein; UIP = usual interstitial pneumonia

Rheumatoid arthritis (RA) is a destructive, systemic, inflammatory disorder¹ that currently affects approximately 1.3 million adults in the United States.² Compared with the general population, median survival in patients with RA is decreased by 10 to 11 years,³ with a major portion of disease burden and excess mortality being due to the extraarticular manifestations present in 40% of individuals with RA.⁴ Interstitial lung disease (ILD) is the most common clinical manifestation of lung involvement in RA,^{1,5–7} with clinically evident disease occurring in about 10% of the RA population. An additional 30% of individuals demonstrate evidence of subclinical disease⁸ on high-resolution CT (HRCT) scans.^{1,9–11} The presence of clinically evident

RA-associated ILD (RA-ILD) has a poor prognosis,¹² accounting for 7% of all RA-associated deaths¹ and contributing to 13% of the excess mortality of patients with RA.⁶ This translates to a risk of death for individuals with RA-ILD that is three times higher than for patients with RA without ILD and a median survival after RA-ILD diagnosis of only 2.6 years.⁶ Studies have demonstrated that even though overall mortality rates for RA are declining, death from RA-ILD has increased significantly,¹ further emphasizing the physical, psychosocial, and economic burden of RA-ILD.

This perspective briefly reviews the current state of knowledge of RA-ILD and proposes a roadmap for future translational research addressing important

existing knowledge gaps (Table 1). We highlight three areas as examples of areas that would benefit from additional research: (1) the diagnosis and evaluation of subclinical RA-ILD, (2) the significance of radiologic and histopathologic subtypes of RA-ILD, and (3) the development of biomarkers. Collaborative cohort development focused on translational research would facilitate diagnosis, improve risk prediction, and allow testing of targeted treatments, ultimately leading to a decrease in the significant morbidity and mortality associated with RA-ILD.

CURRENT STATE OF KNOWLEDGE

Although recognized as an important and prevalent complication of RA, there is no consensus in the literature as to the definition of RA-ILD. Borrowing from the American Thoracic Society/European Respiratory Society statements on the idiopathic interstitial pneumonias (IIPs)¹³ and idiopathic pulmonary fibrosis (IPF),¹⁴ an individual diagnosed with RA-ILD should have an underlying diagnosis of RA as well as evidence of chronic, diffuse interstitial pneumonia on HRCT scan, lung biopsy, or both without other identifiable etiology. This definition helps to distinguish RA-ILD from other forms of parenchymal lung involvement in RA, such

as inflammatory (rheumatoid) nodules, respiratory infections, and treatment-related ILD.

Risk Factors

Although RA itself is a risk factor for the development of fibrotic lung disease, only a subset of patients with RA will develop ILD. Certain factors associated with a higher incidence of RA-ILD include advanced age, male sex, increased severity of joint disease,⁶ high-titer rheumatoid factor (RF),¹⁵ elevated levels of anti-citrullinated protein antibodies (ACPAs),¹⁶ and smoking (shown to be a risk factor for both RA-ILD^{17,18} and fibrotic lung diseases in general).^{14,19-22} Smoking promotes protein citrullination in the lungs, which may lead to generation of ACPA, and promotes lung abnormalities,²³ especially in individuals with the HLA-DRB1 “shared epitope.”²⁴ These findings suggest that anti-cyclic citrullinated peptide (CCP) antibodies²⁵ and HLA-DR serotype are risk factors for the development of RA-ILD.²⁶ The notion that RA may at times “start” in the lungs is suggested by the description of a cohort of patients with anti-CCP positivity and lung disease in the absence of existing RA or other connective tissue disease, some of whom developed articular disease within a short period of follow-up.²⁷ Other potential risk factors associated with the development of RA-ILD include gastroesophageal reflux disease,^{28,29} genetic factors such as MUC5B,^{30,31} surfactant protein (SP) abnormalities,³² or TERT^{33,34} mutations and telomere length.³⁵

Diagnosis

ILD usually arises within the context of well-established RA but can also be the presenting manifestation of RA; as such, in patients presenting with an IIP, the presence of an occult connective tissue disease (CTD), and RA in particular, should be considered.¹⁴ When ILD is identified in established RA, it is important to distinguish between primary or direct, disease-related, ILD and secondary or indirect complications presenting as diffuse lung disease. Primary RA-ILD has well-described histopathologic subtypes that are shared with the IIPs,^{13,14} in particular, usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (Fig 1).^{36,37} Other histopathologic patterns include organizing pneumonia³⁸ and diffuse alveolar damage.³⁹ Indirect complications include treatment-related diffuse lung disease that occurs as an adverse effect of therapy with disease-modifying antirheumatic drugs (DMARDs), infectious complications, and lymphoproliferative disease.⁴⁰ The ability to distinguish between primary RA-ILD and secondary or indirect complications can be challenging and is primarily based on clinical judgment using the entirety of the clinical context, including features of disease presentation,

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Table 1—Future Areas for Investigation in RA-ILD

Area for Investigation	Subclinical Disease	Histopathologic Subtypes	Biomarkers
Diagnosis and risk stratification	Screening	HRCT imaging vs lung biopsy	Single biomarker vs panel
	Symptoms ± PFTs ± HRCT imaging	Use of biomarkers to avoid lung biopsy	Addition to clinical predictive models
	Clinical predictive modeling	Demographic features associated with UIP	Peripheral blood vs alveolar profiling
	Role of biomarkers	Age	Confounding by severity of RA disease and DMARDs, which can also affect biomarker levels
Natural history		Sex	
		Smoking history	
	Impairments at diagnosis	UIP vs non-UIP pattern	Risk for progressive subclinical disease
	Symptomatic (dyspnea)	Rates of progression	Alternative to HRCT imaging for determining disease progression
	Physiologic (PFTs, O ₂ sat)	Prognostication/staging	
	Functional (6MWD)	Acute exacerbations	Role in prognostication/staging
	Radiologic (interstitial lung abnormalities)	Mortality	
	Subset with progressive disease		
	Identification		
	Risk factors		
Management	Prognostication/staging		
	Role of smoking		
	Progressive disease	Tailored treatment	Determine response to therapy
	Routine follow-up	Therapies harmful in IPF may be harmful or helpful in RA-ILD with UIP pattern	Distinguish treatment-related ILD and disease-related ILD
	Earlier treatment	Therapies helpful in CTD-ILD may work in RA-non-UIP	Surrogate end point in clinical trials
	Effect of smoking cessation	Timing of transplant based on subtype	

6MWD = 6-min walk distance; CTD = connective tissue disease; DMARD = disease-modifying antirheumatic drug; HRCT = high-resolution CT; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; O₂ sat = oxygen saturation; PFT = pulmonary function test; RA = rheumatoid arthritis; RA-ILD = rheumatoid arthritis-associated interstitial lung disease; UIP = usual interstitial pneumonia.

temporal association of specific therapy with disease development, and response to stopping the suspected therapeutic agent.⁴¹

Natural History

Subclinical RA-ILD can be defined as specific radiologic, physiologic, and in some cases histopathologic abnormalities in the lungs of patients with RA who are either asymptomatic or have symptoms and physiologic abnormalities that are as yet unrecognized as being due to RA-ILD (Fig 2).⁴² Subclinical RA-ILD is most commonly identified on HRCT imaging of the chest by the presence of specific abnormal imaging features termed interstitial lung abnormalities, which are defined as nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis affecting >5% of any lobar region.^{8,43} In one study, 33% of patients with RA without dyspnea or cough had interstitial lung abnormalities on chest CT scan, and radiologic progression was observed in more than one-half over the next 1 to 2 years,¹⁷ suggesting that progression of asymptomatic radiologic changes could lead to the development of clinically evident RA-ILD. As it is unclear at this time how

earlier detection of RA-ILD impacts disease course or alters treatment decisions, such as timing of immunosuppression and choice of agent, the role of routine chest imaging screening of asymptomatic patients with RA for subclinical RA-ILD is unclear.

A variety of clinical measures have been used to define disease severity and progression and to predict early mortality in clinically evident RA-ILD, most of which have been drawn from the IPF and lung transplant literature and not specifically validated in RA-ILD. These include the extent of honeycombing on HRCT imaging, decrease in diffusing capacity of lung for carbon monoxide (DLCO), longitudinal decline in FVC or DLCO, new onset of desaturation during exercise, presence of pulmonary hypertension, and level of dyspnea.^{14,23,44,45} In clinically evident RA-ILD, there are emerging data to suggest that prognosis may also be related to the underlying histopathologic phenotype, with RA-ILD with UIP pattern having increased mortality compared with non-UIP.^{36,46-51} For example, patients with RA-ILD with UIP pattern have a lower median survival compared with patients with non-UIP pattern, and the HRCT scan pattern of UIP was independently associated with worse survival.⁴⁷ Other investigators have reported episodes of acute exacerbation in patients with RA-ILD with UIP pattern,

FIGURE 1. High-resolution CT (HRCT) and pathologic images of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) with usual interstitial pneumonia (UIP) and non-UIP pattern. A, B, UIP pattern in rheumatoid arthritis (RA). A, This HRCT image demonstrates the reticular opacities, traction bronchiectasis, and basilar/peripheral honeycombing diagnostic of UIP.¹⁴ B, This biopsy specimen of the UIP pattern in RA shows patchy fibrosis with marked fibrosis and microscopic honeycombing in the subpleural region and fibroblast foci at the interface between fibrotic and less-involved lung tissue (hematoxylin and eosin [H&E], magnification $\times 40$). C, D, Non-UIP pattern in RA. C, This image demonstrates some of the HRCT scan changes that would suggest a non-UIP pattern: micronodules, air trapping, nonhoneycomb cysts, extensive ground-glass opacities, consolidation, a peribronchovascular-predominant distribution, or coexistent pleural abnormalities.¹⁴ D, This biopsy of the nonspecific interstitial pneumonia pattern in RA shows diffuse but variable alveolar septal thickening by dense fibrosis and chronic inflammation (H&E, magnification $\times 40$).

but not in those without the UIP pattern.⁵²⁻⁵⁵ Although many of these studies are limited by small sample size, they collectively suggest that the natural history of RA-ILD with UIP pattern parallels that of IPF, with poor survival rates.

Currently, there are two staging systems for RA-ILD proposed in the literature, but their use is limited by lack of prospective validation. The first is based on the Goh et al⁵⁶ staging system for ILD in systemic sclerosis, in which HRCT image-characterized ILD is classified as limited (involving $< 20\%$ of the lung parenchyma), borderline ($20\%-25\%$ lung involvement), or advanced ($> 25\%$ lung involvement). The application of this staging system to RA-ILD demonstrated a better prognosis with limited disease.⁵⁷ The second system suggests dividing individuals with RA-ILD into three broad categories: (1) asymptomatic, incidentally discovered ILD (subclinical disease); (2) limited ILD ($< 20\%$) on HRCT scan with gradually increasing symptoms of dyspnea and slow decline in pulmonary function tests (PFTs); and (3) extensive ILD on HRCT scan with rapidly progressive course and rapidly declining PFTs.²³

Treatment

The optimal treatment of RA-ILD is unclear, as there are no clinical trials, and it is unknown if any treatment is effective in RA-ILD. However, the decision to treat should balance patient-specific factors (age and comorbidities), disease-specific factors (degree of pulmonary impairment, evidence of progression), and the likelihood of response to the chosen therapy. It is important to note that many of these patients will already be on treatment for their synovitis, and in these individuals a diagnosis of RA-ILD may prompt a change in medication, although data to suggest that any agent preferentially targets the joints or lungs are lacking. Treatment initiated specifically for RA-ILD is empirical and, typically, includes corticosteroids, immunomodulating/steroid-sparing agents, or both.⁵⁸ Adjuvant RA-ILD therapies can include smoking cessation, pulmonary rehabilitation, supplemental oxygen, and administration of pneumococcal as well as annual influenza vaccines.⁵⁸ At the same time, both evaluation and treatment should account for comorbidities that can include gastroesophageal reflux disease⁵⁹ and

FIGURE 2. HRCT images of subclinical RA-ILD and RA-ILD. A, B, Interstitial lung abnormalities or subclinical RA-ILD. C, D, RA-ILD. See Figure 1 legend for expansion of abbreviations.

pulmonary hypertension.⁶⁰ Lung transplantation is also an option in the appropriate clinical setting.^{44,61} Most of the DMARDs used to treat articular manifestations of RA (including methotrexate, leflunomide, and biologic agents) have been implicated in the development of pneumonitis at low, but variable, rates.^{17,62-69} If this type of presumed drug-related toxicity occurs, it has been suggested that therapy should be interrupted and, after excluding infection, corticosteroid treatment initiated.⁴¹

SELECTED AREAS FOR INVESTIGATION

Three ongoing areas of investigation in RA-ILD are discussed here to illustrate the need for collaborative translationally focused cohort studies in this disease. There are other areas of study (eg, extrapulmonary/serological manifestations, risk prediction, treatment) that are equally compelling and also deserve attention from the research community.

Subclinical RA-ILD

Approximately one-third of patients with RA will have HRCT imaging evidence of specific pulmonary abnormalities in the absence of respiratory symptoms

indicative of subclinical disease, and a substantial minority will develop clinically evident RA-ILD over time (Fig 2).¹⁷ The significance of subclinical ILD lies not only in its risk of progression but also in its frequent association with physiologic and functional abnormalities that may not be clinically recognized.^{8,17,42,70-72} Consequently, it is possible that some patients with evidence of subclinical RA-ILD may in fact have occult respiratory symptoms, physiologic impairments, and a reduced exercise capacity. Given the widespread use of HRCT imaging in clinical and research settings, we anticipate that an increasing number of pulmonologists and rheumatologists will evaluate and manage subjects with incidentally discovered subclinical RA-ILD on imaging. As such, clinical and translational research needs to focus on a better understanding of the clinical significance of these findings as well as risk factors for its progression to clinically evident disease, as timely completion of this research will enable us to develop a validated approach to the diagnosis, staging, and management of progressive subclinical disease.

Radiographic/Histopathologic Subtyping

Patients with RA-ILD with UIP pattern on lung biopsy or HRCT scan appear to have a distinct clinical, and perhaps biologic, phenotype compared with

patients with RA-ILD without UIP pattern (Fig 1).^{36,38} It remains unclear to what degree RA-ILD with UIP pattern overlaps biologically with IPF. A multicenter randomized controlled trial of patients with IPF conducted by IPFNet found increased rates of death and hospitalization in the intervention group that received a combination of antiinflammatory medications (prednisone, azathioprine, and *N*-acetylcysteine).⁷³ Given the potential pathophysiological overlap of RA-ILD with UIP pattern and IPF, we may need to reconsider the common approach to treatment of RA-ILD with prednisone and other immunomodulatory drugs, although available retrospective data suggest the potential benefit of this approach.⁷⁴ Conversely, once successful IPF therapies are discovered, these could be tested in the subset of RA-ILD with UIP pattern. Beyond these treatment considerations, in future IPF studies, screening with autoimmune markers could help to elucidate the similarities and differences between RA-ILD and IPF. The similarities between these two entities also suggest that RA-ILD with UIP pattern may need to be approached similarly in terms of prognosis and timing of referral for lung transplantation.

In general, these considerations highlight the importance of current efforts to assemble large, multicenter cohorts of patients with RA-ILD with standardized characterization of histopathologic subtype (as well as associated HRCT imaging, functional abnormalities, and biomarker profiles) so that further prognostic comparisons can be made with the IIPs. Specifically, ongoing collection of serial clinical and biologic data in cohorts with well-characterized RA-ILD will facilitate exploration of biologic mechanisms that have been previously identified in IPF (eg, telomere biology,⁷⁵ genetics,^{76,77} endoplasmic reticulum stress,⁷⁸ and epithelial-mesenchymal transition⁷⁹).

Biomarker Discovery

A limited number of RA-ILD biomarkers have been formally examined. These include RF, Krebs von den Lungen-6 (KL-6), and ACPA (including anti-CCP [HSP90] antibodies) (Fig 3A).^{24,26,80} While high-titer RF is associated with the presence of RA-ILD and a decreased DLCO,¹⁵ KL-6 levels have been shown to correlate with severity of CT scan findings.⁸¹ Based on research in other connective tissue disease-related ILD and subclinical ILD, KL-6, SP-A, and SP-D⁸²⁻⁸⁵ appear to be common biomarkers of ILD that may prove useful in the assessment of disease activity and prognosis in RA-ILD (Fig 3B).⁸⁵⁻⁸⁸ Other potential biomarkers of RA-ILD include CC-chemokine ligand-18,^{89,90} CXC chemokine ligand (CXCL)-9, CXCL10, C-reactive protein,⁹¹ IL-6,^{92,93} YKL-40,⁹⁴ CCN2 (connective tissue growth factor),⁹⁵ IL-8, intracellular adhesion

FIGURE 3. Potential biomarkers of RA-ILD. A, Biomarkers drawn from RA-ILD literature. B, Select biomarkers drawn from CTD-ILD, IPF, and subclinical ILD literature. *Based on alveolar profiling of cytokines in BAL fluid. ACPA = anticitrullinated protein antibody; CCL = CC-chemokine ligand; CRP = C-reactive protein; CTD = connective tissue disease; CXCL = CXC chemokine ligand; ICAM = intracellular adhesion molecule; ILD = interstitial lung disease; INF γ = interferon- γ ; IPF = idiopathic pulmonary fibrosis; KL-6 = Krebs von den Lungen-6; MCP = monocyte chemoattractant protein; MMP = matrix metalloproteinase; PDGF = platelet-derived growth factor; RF = rheumatoid factor; SP = surfactant protein; TGF = transforming growth factor; VCAM = vascular cell adhesion molecule. See Figure 1 legend for expansion of other abbreviation.

molecule-1, vascular cell adhesion molecule-1,⁹² and various matrix metalloproteinases (MMPs).^{92,96,97} Furthermore, it has been demonstrated that levels of certain alveolar proteins, including platelet-derived growth factor (PDGF)-AB, PDGF-BB, transforming growth factor- β_2 , and interferon- γ , differed significantly based on the degree of RA-ILD, making this compartment another potential target.¹⁷ This assertion has been further substantiated by the alveolar profiling of cytokines in BAL fluid of individuals with systemic sclerosis, in which IL-8 and monocyte chemoattractant protein-1 were associated with lung fibrosis and prognosis.^{98,99}

We believe that short-term research goals need to focus not only on identification of additional biomarkers in RA-ILD but also on defining the role of these biomarkers in the evaluation of disease mechanisms, diagnosis, prognosis, and/or therapeutic response. In IPF, for example, more recent biomarker studies suggest that a panel of peripheral blood molecular markers, such as MMP7,⁹² SP-A, and SP-D,¹⁰⁰ can complement and enhance the assessment and prognostication of patients when added to established clinical parameters.¹⁰¹ By extension, parallel clinical predictive models incorporating biomarkers may allow us to identify individuals at high risk for developing progressive RA-ILD, thereby facilitating earlier diagnosis as well as monitoring of disease progression and response to therapy. Biomarkers may also play an important role in distinguishing between primary RA-ILD and secondary or indirect causes of diffuse lung disease,¹⁰² in measuring the therapeutic response to treatment,¹⁰³

and in providing surrogate end points for clinical trials.

CONCLUSIONS

RA-ILD is an increasingly recognized and highly morbid condition that is still poorly understood. We have summarized the current state of knowledge in RA-ILD and have provided examples of areas of focus for current and future translational research. Over the next few years, we hope that collaborative research efforts will help to address the current gaps in knowledge regarding diagnosis and management in RA-ILD, potentially leading to improvements in the lives of patients with this debilitating condition. Progress will be catalyzed by the development of large, multicenter longitudinal cohorts of well-characterized patients with matching biologic samples.

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