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Commentary

AHEAD OF THE CURVE

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 disorder[1] 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 disease[8] 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 deaths[1] 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) antibodies[25] 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 pneumonia[38] 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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