Management of Systemic-Sclerosis-Associated Interstitial Lung Disease

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KEYWORDS

• Interstitial lung disease (ILD) • Systemic sclerosis (SSc) • Cyclophosphamide
• Rituximab • Stem cell transplant

KEY POINTS

- Interstitial lung disease (ILD) is the leading cause of mortality for patients with SSc.
- Early diagnosis is critical for managing patients with scleroderma-associated interstitial lung disease (SSc-ILD).
- Pulmonary function tests (PFTs) and high-resolution computed tomographic (HRCT) chest imaging are used for screening and management.
- Immunosuppression can be beneficial, but better therapies are needed.

INTRODUCTION

In the past 35 years, since the introduction of angiotensin-converting enzyme inhibitor therapy as the first effective treatment of scleroderma renal crisis, SSc-ILD has become the leading SSc-related cause of death.[1] In the largest study to date, SSc-ILD accounted for 35% of all disease-related deaths.[2] Thus the management of patients with SSc-ILD is of paramount importance. This article presents a brief discussion of the current knowledge of the pathogenesis of SSc-ILD, because such research may ultimately lead to targeted and more effective management of SSc-ILD. This article then discusses the current state of management of SSc-ILD, beginning with early detection, followed by a discussion of disease staging and risk stratification, and finally a review of current and future treatment options.

The authors have nothing to disclose.

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PATHOGENESIS OF SSC-ILD

Despite several decades of intense investigation, the pathogenesis of SSc-ILD remains unclear. It is likely that SSc-ILD represents a complex interplay between innate and acquired immunity, inflammation, and fibrosis, but the exact sequence of events remains uncertain. As lung biopsy is seldom required to establish a diagnosis of SSc-ILD, insight into the pathogenesis of SSc-ILD has been hampered by a relative lack of access to lung tissue, particularly early in the course of the disease when the greatest insight on disease initiation and mechanisms might be gained. When biopsy is performed, the SSc lung histopathology typically shows interstitial fibrosis with temporal homogeneity and with only a modest inflammatory cell infiltrate (ie, fibrotic nonspecific interstitial pneumonia [NSIP]).[3] Cellular NSIP and usual interstitial pneumonia (UIP) are seen in a smaller proportion of cases.

Recent studies looking at gene expression profiles provide molecular insights into the pathogenesis of SSc-ILD (**Table 1**). Although not completely concordant, lung tissue gene expression and bronchoalveolar lavage (BAL) studies of early- and late-stage SSc-ILD demonstrate abnormal expression of markers of macrophage migration and activation, as well as upregulated expression of transforming growth factor (TGF)-β and interferon-regulated genes.[4–6] Genome-wide association studies have found the gene for chemokine (C-X-C motif) ligand 4 (CXCL4), among others, to be highly and differentially expressed in certain patients with SSc, and a recent proteome-wide analysis found serum levels of CXCL4 to be correlated with lung fibrosis.[7] Polymorphisms at loci for additional genes have also been reported to be associated with the presence and/or severity of pulmonary fibrosis (see **Table 1**).[3,8] Such genetic and molecular insights will likely lead to the future development of predictive serum biomarkers, as well as the development of safe and targeted therapies for patients with SSc-ILD.[3,9]

CLINICAL MANIFESTATIONS

Pulmonary involvement is common, occurring in over 80% of patients with SSc, and is often a significant source of morbidity and mortality.[10] Lung involvement can occur in all subsets of the disease including limited cutaneous SSc, diffuse cutaneous SSc, and SSc sine scleroderma, and it can affect all aspects of the respiratory tract including the parenchyma, vasculature, airways, pleura, and musculature.[11]

Table 1
Gene expression and associations with SSc-ILD

Proposed Biologic Function	Associations with SSc-ILD
Alveolar epithelial homeostasis	SP-B, HGF
Immune regulation	IRAK-1, IRF-5, NLRP1, CXCL4, OAS1, IFI44, CCL18, CD163
Fibroblast activation/matrix remodeling	COL1A, CTGF, MMP-12

Abbreviations: CCL18, chemokine [C-C motif] ligand 18; CD163, cluster of differentiation 163; COL1A, collagen, type I, alpha I; CTGF, CCN2 or connective tissue growth factor; CXCL4, chemokine [C-X-C motif] ligand 4; HGF, hepatocyte growth factor; IFI44, interferon-induced protein 44; IRAK-1, interleukin-1 receptor-associated kinase 1; IRF5, interferon regulatory factor 5; MMP-12, matrix metalloproteinase 12; NLRP1, NACHT, LRR, and PYD domains-containing protein 1; OAS1, 2′,5′-oligoadenylate synthetase 1; SP-B, surfactant protein B.

Adapted from Herzog EL, Mathur A, Tager AM, et al. Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis. How similar and distinct? Arthritis Rheumatol 2014;66:1973; with permission.