DR RAJAIE NAMAS (Orcid ID : 0000-0003-0353-895X)

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Management of Systemic Sclerosis-associated Interstitial Lung Disease in the Current Era

Sogol Sara Amjadi[1], David Roofeh[2], Rajaie Namas[3], Dinesh Khanna[2]

Affiliations:

1: Dignity Health, Henderson, NV

2: Scleroderma Program, University of Michigan, Ann Arbor, MI, USA

3: Cleveland Clinic, Division of Rheumatology, Ab Dhabi, UAE

Corresponding author:

Correspondence to Dinesh Khanna, MD, MSc, Department of Internal Medicine, Division of Rheumatology, 300 North Ingalls St., Suite 7C27, Ann Arbor, MI 48109-5422, USA. Tel: +1 734 763 7182; fax: +1 734 936 3695; e-mail: khannad@umich.edu

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Interstitial Lung disease (ILD) is a group of diseases describing thickening of the interstitium surrounding pulmonary alveolar walls due to underlying inflammation. ILD is often associated with connective tissue diseases. Amongst connective tissue disease related ILDs, 80% of systemic sclerosis (SSc) patients develop ILD[1] with associated morbidity and mortality[2], although a large proportion may not develop clinically significant disease. Screening, early diagnosis and treatment of systemic sclerosis associated ILD (SSc-ILD) is important as up to 33% of SSc-related deaths are attributed to ILD[3] and initiating treatment early in the course of the disease has been shown to slow the progression of disease[4,5]. This article summarizes the risk factors for SSc-ILD and best practices for diagnosis and treatment of SSc-ILD.

Risk Factors and Screening

The goal of treatment in SSc-ILD is prevention of progression where progression is defined as new or worsening symptoms, increase in the extent of pulmonary fibrosis on high resolution computed tomography (HRCT) and/or by a decline in pulmonary function tests (PFTs)[6,7]. This highlights the need for identifying patients at risk of disease progression before worsening occurs. The risk factors for progressive ILD are shown in the Table. Although no absolute risk factors have been identified, these risk factors have been reported to be associated with progressive ILD in patients with SSc.

The risk of developing ILD is greatest early in the course of the disease and the most rapid decline in lung function (forced vital capacity (FVC)) occurs within the initial 3-5 years of disease onset[5]. In addition, the extend of lung involvement on HRCT at baseline combined with reduced or declining FVC and diffusing capacity of the lung for carbon monoxide (DLCO) is predictive of mortality [6,8–10]. Currently, the diagnosis of SSc-ILD is based on characteristic findings of increase reticulations with or without ground glass opacity on HRCT of the chest, irrespective of PFT results. Therefore, it is recommended that all patients with SSc receive HRCT at baseline[11,12]. Additionally, all patients should be evaluated for the evidence of cardiac involvement including assessment for pulmonary hypertension at the initial visit[13].

Due to concern for radiation exposure with repeated HRCT, evaluation of lung function via spirometry and DLCO is recommended every 4-6 months in the first 3-5 years of the disease onset as this has been shown to provide valuable information about disease trajectory[6,14,15].

Treatment

The concepts for management of autoimmune ILD, including SSc-ILD, is shown in the Figure. Not every patient with SSc-ILD requires treatment. Since early SSc-ILD is driven by immune activation and inflammation, current approach involves the use of immunosuppressive therapy with goal of initiation early in the disease to prevent advanced fibrotic disease[16]. Our group has recently published single center recommendations on the management of SSc-ILD[17]. One

strategy is to stratify patients by their lung disease severity (subclinical [defined as minimal ILD on HRCT, normal or near normal FVC and DLCO with no symptoms attributable to ILD] vs. clinical ILD). For those with subclinical ILD, one may initiate therapy for ILD, especially with high-risk features or monitor closely for progressing symptoms, PFTs, and with repeat HRCT if necessary[17]. Current practice involves treating patients on a case by case basis and only after careful review of risks versus benefits as there is significant toxicity associated with some of the available medications.

The treatment for SSc-ILD has included the use of immunosuppressive therapies, in particular cyclophosphamide (CYC) and mycophenolate mofetil (MMF). MMF is largely used in North America and UK for the management of SSc-ILD and it is generally given as 3000 mg/day in divided doses. This is based on the Scleroderma Lung Study II which showed that treatment with MMF offers comparable efficacy as oral CYC and has a better safety profile [18].

Recent data from a Phase 3 trial showed that the treatment of early ILD (mean FVC% of 82% with mild ILD on HRCT) in high -risk populations (early diffuse cutaneous SSc and elevated C-reactive protein with 50% having positive anti-SCL-70 ab) with tocilizumab led to stabilization of FVC% versus a decline of 6.5% in the placebo group at 48 weeks[19]. Similarly, an open-label trial of patients with early diffuse cutaneous SSc and positive anti- SCL-70 found improvement in FVC% at 24 weeks with the use of 2 courses of rituximab (1000 mg x 2 doses) vs. monthly pulse CYC[20]. We offer treatment to patients with subclinical ILD and elevated CRP and/or positive anti- SCL-70.

Other therapy includes autologous hematopoietic stem cell transplantation (HSCT). Several trials have shown that HSCT following immunosuppressive has a beneficial effect in some patients with diffuse cutaneous SSc with multi-organ involvement[21]. The appropriate patient has early disease with progressive ILD and is not responding to immunosuppressive therapy. The goal is to target aggressive and reversible disease.

As shown in the Figure, a clinician may consider anti-fibrotic therapies in patients with progressive ILD or those intolerant of immuno-modulatory therapy (e.g., due to recurrent infections). The SENSCIS trial, a large Phase 3 trial, demonstrated a lesser decline in FVC with the addition of nintedanib (an intracellular multiple tyrosine kinase inhibitor) to background MMF or no therapy vs. placebo[22]. Based on published data, sequential combination therapy could be considered for patients with high risk of progression (not addressed in the SENSCIS

trail), where progression has occurred under monotherapy, or contraindication to the immunosuppressive therapy.

Demographics
Male Gender

In addition to above, comorbid conditions including infections and gastrointestinal disease/ gastro-esophageal reflux disease (GERD) leading to chronic aspiration should be considered in patient with SSc-ILD. In addition to treatment of GERD, appropriate immunization, supplemental oxygen to keep saturations above 88%, and education on tobacco cessation should be part of every patient's ongoing care. Lastly, pulmonary rehabilitation may be effective for some patients[23].

Conclusion/summary

Aside from autologous hematopoietic stem cell transplant, there is limited evidence to support a mortality benefit among SSc–ILD treatments and the benefits of all treatment strategies including combination therapies will need to be weighed against their side effects. Current management includes immunosuppressive therapy in those with subclinical ILD with high risk features or those with clinical ILD. Anti-fibrotics should be considered in those with progressive ILD despite being on immunosuppressive therapy or if there is contraindication to immunosuppressive therapy. Ongoing trial of Scleroderma Lung Study III is assessing if upfront combination of MMF and pirfenidone (anti-fibrotic) is more efficacious than MMF alone in early SSc-ILD (https://medicine.umich.edu/sites/default/files/content/downloads/SclerodermaLungStudies-August2019-Final.pdf).Future research in SSc-ILD should aim at developing tools to identify patients at risk of progressive SSc-ILD and assess appropriate timing and treatment sequence in patients with SSc.

Table. Risk Factors for Progressive Interstitial Lung Disease in Systemic Sclerosis°

African American Ethnicity
Disease Type
Diffuse cutaneous SSc*
Biomarkers
Anti-SCL 70/anti-topoisomerase Ab**
Anti-nucleolar ab (representing AntiTh/To, U3RNP)
C-reactive protein/ Interleukin-6
Chemokine (C-C motif) ligand (CCL-18)
Krebs von den Lungen Protein (KL6)Δ
Surfactant protein D (SP-D)Δ

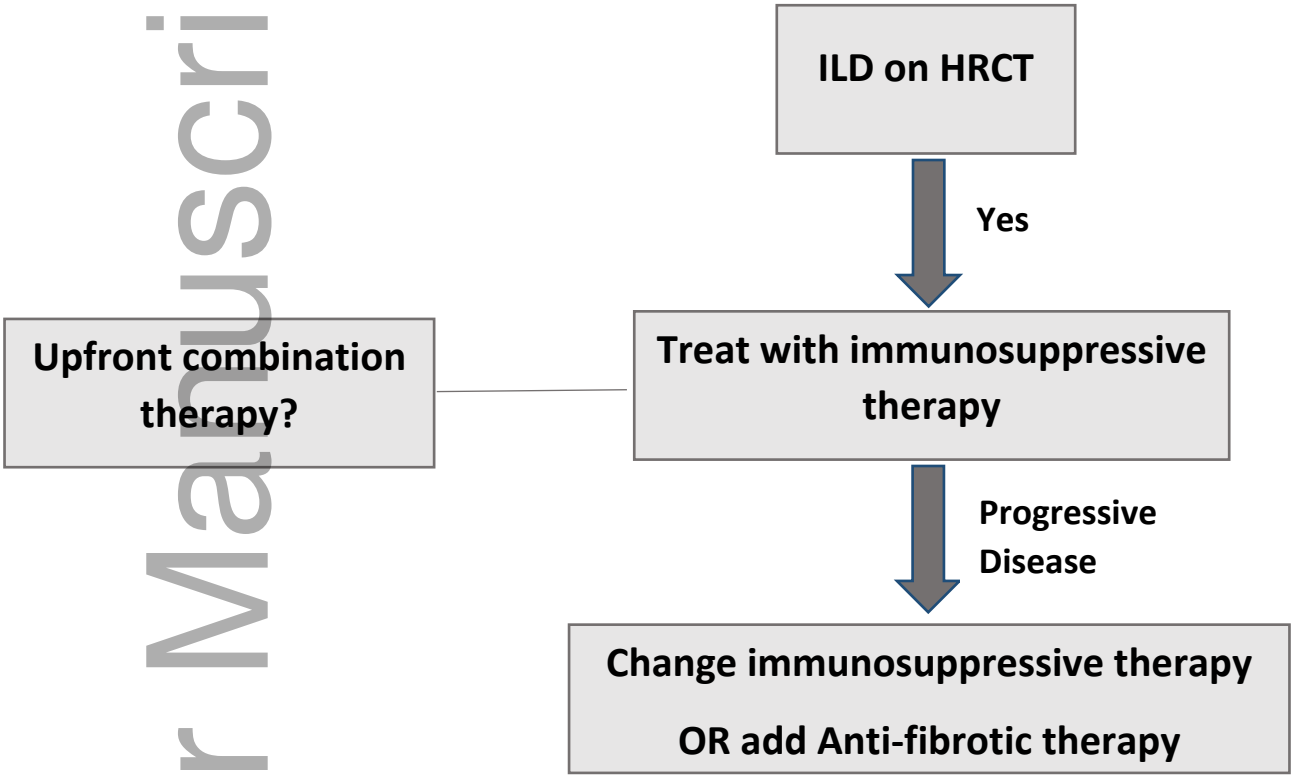
°Recently Reviewed in Khanna et. al.[1]

* SSc: Systemic Sclerosis

** Anti-SCL 70: anti-scleroderma antibody

Δ CCL-18, KL6 and SP-D are serum markers for endothelial injury

Figure. Overview of Management of Systemic Sclerosis Associated Interstitial Lung Disease



HRCT: High Resolution Computed Tomography; ILD: Interstitial Lung Disease

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