Fact Sheet

Pulmonary Fibrosis in Systemic Sclerosis: Diagnosis and Management

National Scleroderma Foundation

Pulmonary disease is an important component of systemic sclerosis (SSc). It is estimated that 90% of patients with SSc have some evidence of pulmonary disease[1]. This makes pulmonary disease second only to esophageal disease as the most common manifestation of SSc found on the inside of your body (visceral) component.

Moreover, pulmonary involvement portends a poorer prognosis and pulmonary disease is now the leading cause of death amongst patients with SSc with an estimated mortality from pulmonary disease of all causes to be 33%[1]. While multiple pulmonary manifestations have been associated with SSc including pleural effusions[2], bronchiectasis[3], lung neoplasms[4], aspiration pneumonia and drug induced pneumonitis, the most common pulmonary manifestations of SSc include pulmonary hypertension and interstitial lung diseases (ILDs). The significant prevalence of ILD in SSc is reflected in the classification criteria of SSc [2] with the finding providing 2 points towards diagnosis of SSc.

Lung Fibrosis in SSc

Like pulmonary fibrosis of most origins including idiopathic pulmonary fibrosis, the precise molecular events that occur in the pathogenesis of lung fibrosis is not well understood. There is likely a complex interplay between inflammatory[5], antibody production[6-7], oxidative stress and fibrosis occurring in the setting of blood vessel hyperreactivity[8].

Environmental or genetic factors may contribute to the development of ILD in SSc and researchers are actively trying to identify these targets[3]. While environmental triggers have been considered in the pathophysiology of SSc in general and environmental exposures such as polyvinylchloride, and an impurity in one

preparation of L-tryptophan have been known to trigger scleroderma like syndromes, there has never been a clearly established environmental link. The lung injury specific to inhalation of inorganic or organic dusts in the environment are termed pneumoconiosis or hypersensitivity pneumonitis, which are not the same as ILD. There has never been an environmental exposure implicated specific to ILD associated with SSc.

A genetic contribution to scleroderma is supported by observed familial aggregation, ethnic predispositions, gene association studies and genome wide studies[9]. Pedigrees have been described that demonstrate members with SSc as well as members with ILDs not known to be related to SSc in numbers higher than would be expected by chance, suggesting a shared genetic predisposition between SSc, SSc ILD and non SSc[10]. As with all genetic studies, the heterogeneous nature of SSc complicates the detection and interpretation of genetic studies and better characterization of phenotype may aid the understanding of scleroderma in general and the development of ILD specifically[9].

Subsets of Scleroderma Associated with ILD

The estimated prevalence of ILD in SSc ranges from 25-90% depending on the methods utilized and the subset of SSc patients evaluated. There are currently no reliable means to consistently predict which SSc patients will develop ILD. There are some clinical predictors that have been associated with a higher prevalence of ILD. These include African American ethnicity, higher skin score (diffuse cutaneous, dcSSc), muscle inflammation (elevated serum CPK levels), hypothyroidism, and cardiac involvement[12].

The association between SSc and ILD is strongest in patients who suffer from dcSSc. Patients with diffuse SSc typically develop the ILD early in the course of their disease. However, ILD is also has a well described association with limited skin involvement (lcSSc)[13]. Specific autoantibodies such as the anti-SCL-70, RNP, anti U11/ U12 RNP, anti Th/ To and antihistone antibodies have been reported to be associated with an increased risk of ILD in SSc[14] and others such as anticentromere antibodies are protective[15]. However, these associations are not specific are not absolutely predictive and serologies have low sensitivity[13] limiting the effectiveness of the serologies as a clinical predictor of ILD.

Diagnosis of ILD in SSc

The onset of ILD in scleroderma is often difficult to detect. Factors that may mask the onset of disease include mild lung involvement, musculoskeletal, or hematologic (such as anemia) manifestations of SSc or other comorbid conditions. When studied systematically, approximately 50% of patients with ILD will demonstrate a measurable decline in pulmonary function within the first three years of diagnosis of SSc although many of these patients report no pulmonary symptoms[16]. Once the presence of a pulmonary disease is established, care must be taken to differentiate between ILD and other pulmonary manifestations, specifically pulmonary arterial hypertension (PAH), which may co-exist with ILD or be present in the absence in ILD. Thus, it is clear that correctly identifying and managing ILD in scleroderma is a critical issue in the management of SSc.

There are a number of tests that can be applied to the diagnosis of ILD in SSc. Physical examination can be revealing with the presence of bibasilar crackles, but often times these are subtle or absent early in the disease. Thus, additional testing is required to assess for the presence of ILD in SSc.

Pulmonary Function Testing

Pulmonary function testing (PFTs) are cornerstone tests in the evaluation of dyspnea and for detection of pulmonary involvement in patients with SSc. While not diagnostic of ILD, patients with ILD will demonstrate restriction on lung function testing. Total Lung Capacity

(TLC) by means of plethysmography is the most reliable measure of restriction and will confirm the presence of true lung restriction. However, spirometry is more typically utilized in clinical practice provides a good estimation of true restriction. Spirometry provides measures of the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1). In a restrictive lung disease, the FVC should be reduced and the FEV1/FVC ratio should be normal.

The diffusing capacity (DLCO) provides a measure of gas transfer between the air inhaled into the alveoli to the red blood cells in the systemic circulation. The DLCO is one of the most valuable measures in the evaluation of the scleroderma patient as a decreased value may be the earliest signal of lung disease in SSc and is reduced in 70% of SSc patients[17-18]. Moreover, the DLCO correlates most closely with the degree of disease seen on the high-resolution computed tomography (HRCT) scan[19]. The DLCO will be reduced in both pulmonary hypertension and ILD. Thus, the DLCO is not specific for the diagnosis of SSc ILD, but does indicate further evaluation is indicated.

The rate of decline of both the FVC and the DLCO are important prognosticators of survival[16, 19]. The most rapid decline in the FVC occurs within the first three to five years of disease onset[16]. This implies that lung injury is an early event and suggests that frequent monitoring in lung function in early-stage disease is important.

High Resolution CT

As with ILDs of all types, the HRCT is the most sensitive and specific modality for detecting and characterizing any ILD present in the setting of SSc. It is more sensitive than chest radiograph and is the imaging technique of choice[20]. The most common radiographic pattern is that of NSIP. Early in the disease, ground glass opacities are prominent in a peripheral distribution and then progress to reticular changes. The classic UIP pattern with bibasilar reticulation, traction bronchiectasis and honeycombing is also observed in patients with SSc but less commonly than NSIP. Honeycombing is seen more frequently in patients with lcSSc than in those

with diffuse SSc[21]. Tracheobronchial disease can be seen in patients with an overlap of Sjögren's syndrome, A HRCT is required to make these radiographic distinctions.

The HRCT scan has limited prognostic significance. The finding of ground glass opacities does not universally connote reversible disease or alveolitis and is often fine reticulation below the threshold of CT detection[22]. The extent of ILD seen on HRCT has prognostic significance with those patients demonstrating more than 20% involvement demonstrating increased mortality[23]. There are several computer-aided tools in development to help better understand meaningful change on HRCT scan, but these are mainly research tools. Additionally, the role of low radiation dose HRCT and lung ultrasound for serial monitoring the progression of ILD is also under investigation.

Bronchoalveolar Lavage (BAL)

The role of BAL in patients with SSc ILD is controversial and most often utilized when there is concern about infection, malignancy, or drug toxicity. When a cell count is done on BAL from patients with SSc-associated ILD, elevated numbers of granulocytes may be seen, especially neutrophils and eosinophils. Increased numbers of lymphocytes and mast cells may also be seen[24]. Early studies correlated increased granulocytes in BAL with increased response to immunosuppression presumably because this represented active alveolitis[25-26]. Subsequently, BAL granulocytosis has been shown to correlate with the degree of ground glass opacity seen on HRCT[21] and with more advanced interstitial disease[27]. However, data from the Scleroderma Lung Study suggest that BAL granulocytosis does not add any additional prognostic information to HRCT and pulmonary function measures and is not a predictor of treatment response[27-28]. There is no question that BAL is an important test in the consideration of infection, especially when a patient is taking medications that suppress the immune system.

Biopsy

Similar to radiographic appearances, there are a variety of histologic subtypes found in SSc ILD. NSIP is seen most commonly, estimated to be the histopathology in 76% of the cases[19]. In this same series, UIP occurred in 11% of the cases and there were rare cases of organizing pneumonia and diffuse alveolar damage. Importantly, the clinical outcome does not correlate with the observed histology[19, 29]. Patients with scleroderma ILD can often experience stabilization after the initial development of their lung disease. These patterns are in stark contrast to idiopathic ILDs where UIP is the most common pathology, the pathologic finding of UIP is associated with a poorer prognosis and stabilization of UIP for decades is rarely seen. Specifically, in a series of 80 patients, survival does not differ between cellular NSIP, fibrotic NSIP and UIP. Thus, histology has no prognostic value. Given this data, there is rarely value to a surgical biopsy in the evaluation of a patient with scleroderma associated ILD. The exception to this may be in cases of an unusual CT pattern, which does not fit a predicted pattern seen in SSc.

Treatment of ILD in SSc

The decision of who requires treatment in the ILD associated with SSc is not always simple. The goals of therapy are to provide an effective agent to a patient in order to prevent progression to fibrosis and to target active inflammation or alveolitis as this may represent a reversible component of the disease. A patient's symptoms of shortness of breath and cough are important.

Thus, the appropriate candidates for therapy are those who have symptoms, early-stage lung disease, ground glass opacities on CT scan or who are demonstrating progression of disease.

It is notable that therapeutic interventions remain primarily anti- inflammatory in nature as inflammation is still believed to be the primary driver of lung disease progression. This is in contrast to the IPF model where inflammation is felt to be less important than an aberrant fibrotic pathway. Only a small number of drugs have been assessed via randomized controlled studies and few therapeutic options exist for patients with SSc ILD.

Nintedanib

The Food and Drug Administration (FDA) approved the first specific therapy for SSc-ILD, following a randomized, double- blind placebo-controlled trial among patients with

ILD associated with SSc that showed that the annual rate of decline in FVC was lower with nintedanib than with placebo. While no clinical benefit of nintedanib was observed for other manifestations of SSc, nintedanib, a tyrosine kinase inhibitor, demonstrated antifibrotic and antiinflammatory effects.

Cyclophosphamide

This drug has been rigorously assessed for use in SSc ILD. In general, there is evidence that it has a small benefit for long stabilization by PFT and breathlessness (PMID 29297205) . The Scleroderma Lung Study (SLS) 28 was a double-blind, 13 center trial of 158 patients with early SSc-associated ILD who demonstrated evidence of active alveolar inflammation with either ground glass opacities on HRCT or increased cellularity on BAL. Patients were randomized to receive either oral cyclophosphamide (≤2 mg/kg) or placebo daily for one year. In this study, the cyclophosphamide group had a smaller decline than the placebo group (-1.0 versus -2.6 percent predicted). This difference, while small, was statistically significant. This difference was seen at the end of the first year of treatment. In addition, a HRCT scan study was done on a subset of the SLS patients. With comparison of the initial CT scan and follow-up CT scan at one year, less progression of fibrosis was seen in the cyclophosphamide group[30].

Cyclophosphamide is an effective, albeit with small impact, agent for treatment of SSc associated ILD, there are several additional considerations. There is significant toxicity associated with daily oral cyclophosphamide including blood in the urine (hematuria), low blood counts (cytopenias), and malignancies. There is also concern that the response seen at one year is not persistent. While patient's reports of respiratory symptomatology and objective skin improvements were still present at the 24-month SLS follow-up study, the differential improvement in FVC had disappeared[31].

IV administration of cyclophosphamide is less rigorously studied but several uncontrolled studies[32-34] and one randomized trial have been done. In the 45 patient double blind placebo-controlled study, there was a trend toward improved FVC in the cyclophosphamide group but this did not achieve statistical significance[35]. Thus, it remains unclear what the true role of IV cyclophophamide might be in the management of SSc related ILD.

Mycophenolate Mofetil

Mycophenolate is an inhibitor of lymphocyte proliferation. This drug has been the subject of retrospective studies and observational studies. These small studies have had mixed results but observed improvements in FVC and DLCO have been documented[36-38]. The second Scleroderma Lung Study (SLS II) compared in a double-blind fashion 142 SSc-ILD patients with 7 years disease duration or less to receive either mycophenolate mofetil (MMF) (n = 69) for 2 years or oral cyclophosphamide (n = 73) for 1 year followed by a year of placebo treatment. This study showed equivalence for both therapies, but MMF was better tolerated.

Rituximab

The monoclonal antibody rituximab depletes B cells that play in the pathogenesis of SSc. In a randomized controlled trial in 14 patients with SSc-ILD, rituximab (4 weekly infusions followed by 4 weekly infusions at 24 weeks) was associated with significant improvement in both FVC(%) and DLCO(%) at 1 year. Case control studies with anti–B-cell therapy were associated with stability or improvement in pulmonary function tests. In these studies, the medication was well tolerated. However, a recent prospective cohort study of 254 patients treated with rituximab compared with 9575 propensity-score–matched patients showed that treated patients did not have significantly different rates of decrease in FVC or DLCO, although they were more likely to have improvement in skin fibrosis. More data is needed to fully evaluate the efficacy of rituximab in SSc-ILD. Currently, there are 2 clinical trials of rituximab in patients with ILD connective tissue disease that are currently recruiting patients (clinicaltrials.gov: NCT02990286 and NCT01862926).

Intravenous Immunoglobulin

Intravenous Ig (IVIg) is a pooled plasma product that is sometimes used in SSc patients with ILD and inflammatory muscle disease (myositis). It is sometimes used off-label with increasing

frequency for refractory cases that have failed to respond to immunosuppression. Although associated with less systemic toxicity and global immunosuppression than traditional agents, IVIg is much more costly.

Corticosteroids

The role of corticosteroids remains unclear in SSC related ILD. In general, these drugs are avoided because of the well-known risk of scleroderma renal crisis. This phenomenon has been well documented[39] and occurs at low prednisone doses with a mean dose of only 7.4 mg in one series[40]. However, in most clinical trials, use of prednisone was permitted with the drug in question. Thus, while monotherapy with glucocorticoids is not recommended, the role that the accompanying prednisone plays in combination with cyclophosphamide, mycophenolate or other therapies remains unknown.

Other therapies

There are a large number of other possible therapies that are under investigation. Beyond the consideration of inflammation as the primary driver of lung fibrosis, other pathways have been targets of study. The anti-fibrotic effects of pirfenidone are under investigation in SLSIII, which is a Phase II multi-center, double-blind, parallel group, randomized and placebo-controlled clinical trial addressing the treatment of patients with active and symptomatic SSc-ILD. Patients who are either treatment naive or only recently started treatment (</= 6 months of prior treatment) will be randomized in a 1:1 assignment to receive either oral mycophenolate mofetil (MMF) and a placebo or a combination of oral MMF and oral pirfenidone, with both regimens administered for 18 months.

Conclusion

ILD in SSc is a common manifestation that is associated with poor prognosis.

Careful evaluation by the clinician is warranted to detect the presence of an ILD and to select patients for consideration of therapy. Factors to consider in the initiation of therapy include early disease, evidence of progression and evidence of alveolitis. Possible side effects of therapy must be weighed against the known benefits. At the current time, nintedanib, cyclophosphamide and mycophenolate mofetil remain the best studied therapeutic agents although alternatives are actively being evaluated. The role of other immunosuppressive agents or other pathways remains undetermined and offer hope for future therapeutic interventions, but there is some evidence for rituximab, tocilizumab, and pirfenidone. More data is necessary to best understand the role of these agents for SS-related ILD. For some patients with access to specialty centers hematopoietic stem cell transplantation and lung transplantation may be an option. Additional research is needed to determine which patients will benefit from SSc-ILD therapy, how to best measure their treatment response, and long- term management plans after initial therapy in order to optimize outcomes among patients with SSc-ILD.

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