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Careful evaluation by the clinician is warranted to
5. Atamas SP, Yurovsky VV, Wise R, et al. Production of type 2 cytokines by
8. Tamby MC, Chanseaud Y, Guillevin L, Mouthon L. New insights into the
disease in limited scleroderma: histopathology, clinical features, and survival.
disease in systemic sclerosis: relation to classification based on extent of
11. Seibold JR, Denton CP, Furst DE, et al. Randomized, prospective, placebo-
39. Steen VD, Medsger TA, Jr. Case-control study of corticosteroids and other drugs
38. Swigris JJ, Olson AL, Fischer A, et al. Mycophenolate mofetil is safe, well
27. Strange C, Bolster MB, Roth MD, et al. Bronchoalveolar lavage and response to
43. Gordon J, Spiera R. Tyrosine Kinase Inhibitors in the Treatment of Systemic
41. Seibold JR, Denton CP, Furst DE, et al. Randomized, prospective, placebo-
33. Griffiths B, Miles S, Moss H, Robertson R, Veale D, Emery P. Systemic
thoracic high-resolution CT scan than placebo: findings from the scleroderma lung
disease with cyclophosphamide is associated with less progressive fibrosis on serial
collagen vascular diseases: comparison of the clinical characteristics and prognostic
cyclophosphamide in scleroderma interstitial lung disease. Am J Respir Crit Care
Vlachoyiannopoulos PG. Cyclophosphamide with low or high dose prednisolone
treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa,
fluid in scleroderma interstitial lung disease: technical aspects and clinical

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Pulmonary disease is an important component of systemic sclerosis (SSc). It is estimated that 80% of patients with SSc have some evidence of pulmonary disease. This makes pulmonary disease second only to esophageal disease as the most commonly seen 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%9. While multiple pulmonary manifestations have been associated with SSc including pleural effusions3, bronchiectasis3, lung neoplasms4, 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 criteria of the diagnosis of SSc with the finding of predominantly basilar fibrosis being one of the three minor criteria utilized by the American College of Rheumatology for the 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 inflammatory5, antibody production6,7, oxidative stress and fibrosis occurring in the setting of blood vessel hyperreactivity8.

It is unclear what environmental or genetic factors may contribute to the development of ILD in SSc. 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. Moreover, 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 studies9. 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 SSc10. 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 specifically9.
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\textsuperscript{11}. 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 and serum CPK levels, hypothyroidism, and cardiac involvement\textsuperscript{12}.

The association between SSc and ILD is strongest in patients who suffer from diffuse SSc. 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 lcSSC\textsuperscript{13}. Specific auto-antibodies 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\textsuperscript{14} and others such as anticentromere antibodies are protective\textsuperscript{15}. However, these associations are not specific are not absolutely predictive and serologies have low sensitivity\textsuperscript{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\textsuperscript{16}. Once the presence of a pulmonary disease is established, care must be taken to differentiate between ILD and other pulmonary manifestations, specifically 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. Patients with interstitial lung involvement 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. Moreover, the DLCO correlates most closely with the degree of disease seen on the high resolution computed tomography (HRCT) scan. The DLCO will be reduced in both pulmonary hypertension and ILD. Thus, the DLCO is not specific for the diagnosis of SSC ILD.

The rate of decline of both the FVC and the DLCO are important prognosticators of survival. The most rapid decline in the FVC occurs within the first three to five years of disease onset. 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. 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 scleroderma but less commonly than NSIP. Honeycombing is seen more frequently in patients with limited SSC than in those with diffuse SSC. 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. The extent of ILD seen on HRCT has prognostic significance with those patients demonstrating more than 20% involvement demonstrating increased mortality.

**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. Early studies correlated increased granulocytes in BAL with increased response to immunosuppression presumably because this represented active alveolitis. Subsequently, BAL granulocytosis has been shown to correlate with the degree of ground glass opacity seen on HRCT and with more advanced interstitial disease. 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. There is no question that BAL is an important test in the consideration of infection.

**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. 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. 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. Thus, the appropriate candidates for therapy are those who have early stage lung disease, have 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.

**Cyclophosphamide**

This drug has been the most rigorously assessed for use in SSc ILD. The Scleroderma Lung Study (SLS) 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.

While these results suggest that 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 cytoxan including hematuria, 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.

IV administration of cyclophosphamide is less rigorously studied but several uncontrolled studies and one randomized trial have been done. In the 45 patient double blind placebo controlled study, there was a
Lung Fibrosis in SSc

The onset of ILD in scleroderma is often difficult to predict. To correctly identify and manage ILD in scleroderma, care must be taken to differentiate between ILD and other pulmonary manifestations, specifically PAH which may co-exist with ILD or be present in the absence of ILD. Thus, it is clear that correctly identifying and managing ILD in scleroderma is a critical issue in the management of SSc.

There is likely a complex interplay between inflammatory, fibrotic, and pulmonary disease. The precise molecular events that occur in the lung in SSc are not fully understood. While lung biopsy remains the gold standard for the diagnosis of ILD, it is a invasive procedure with significant morbidity. Furthermore, histology is not always diagnostic of ILD. The most commonly seen visceral component. Moreover, the DLCO will be reduced in both pulmonary hypertension and PAH. The rate of decline of both the FVC and the DLCO are limited by the effectiveness of the serologies as a clinical predictor of ILD.

The most common radiographic pattern is that of NSIP. Biopsy has been assessed via randomized controlled studies and few true restriction. Spirometry provides measures of the true restriction. However, spirometry is more typically utilized in clinical practice provides a good estimation of true restriction. When studied systematically, approximately 70% of SSc patients report no pulmonary symptoms. Once the presence of a pulmonary disease is established, care must be limited to consistent prediction which SSc patients are susceptible to pulmonary involvement. When ILD is diagnosed, 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 correlates with the degree of ground glass opacity on HRCT. Similar to radiographic appearances, there are a variety of histological patterns. Biopsy has been assessed via randomized controlled studies and few true restriction. However, spirometry is more typically utilized when there is concern about pulmonary involvement.

Histology has no role in predicting survival. The most rapid decline of lung function has been associated with those patients demonstrating more than 20% predicted pattern seen in SSc. The most rapid decline of lung function has been associated with patients demonstrating more than 20% predicted pattern seen in SSc. The most rapid decline of lung function has been associated with patients demonstrating more than 20% predicted pattern seen in SSc. The most rapid decline of lung function has been associated with patients demonstrating more than 20% predicted pattern seen in SSc. The most rapid decline of lung function has been associated with patients demonstrating more than 20% predicted pattern seen in SSc.

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Bronchoalveolar Lavage (BAL)

Study suggest that BAL granulocytosis does not add to the diagnostic accuracy of ILD in scleroderma. When ILD is diagnosed, the FVC should be reduced and the FEV1/FVC ratio should be normal. In this study, the cyclophosphamide group had a significant improvement in pulmonary function compared to the placebo group. In addition, a HRCT scan study was done on a subset of the SLS patients. The most rapid decline of lung function has been associated with patients demonstrating more than 20% predicted pattern seen in SSc.

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When you become a member of the Scleroderma Foundation, you support the organization’s mission of support, education and research. Your donation helps pay for programs in each of those three areas, including:

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low prednisone doses with a mean dose of only 7.4 mg. Prednisone plays a role in combination with cyclophosphamide, imatinib was associated with a statistically significant improvement in IPF-42.

Secondary end points of time to death and distance walked were not significantly different between groups. However, the primary endpoint of a change in six-minute walk distance was significantly improved in the bosentan group compared to the control group (25.4 meters vs. 12.3 meters, p<0.05). Bosentan for ILD was recently studied in a randomized controlled trial in progressive systemic sclerosis with poor prognosis.

Endothelin receptor antagonists have been effective in other pathways, but their role in SSC remains undetermined. Beyond the consideration of inflammation as the primary driver of lung fibrosis, other pathways have been targets of study.

The role of corticosteroids remains unclear in SSC. Small studies have had mixed results but observed benefits. At the current time, cytoxan remains the best initiator of therapy, but its effects of therapy must be weighed against the known side effects of therapy.

Mycophenolate Mofetil was associated with a statistically significant improvement in IPF-42. However, the improvement did not achieve statistical significance compared to the control group. Scleroderma Lung Study II as a possible alternative to cyclophosphamide might be in the management of SSC.

In general, these drugs are avoided because of their side effects. In pneumoconiosis, patients often have a worse prognosis and the use of these drugs is controversial. Related ILD is a common manifestation that is associated with poor prognosis.

In diffuse systemic sclerosis, pulmonary fibrosis is common. Chest CT is a useful tool for diagnosis and monitoring disease progression. Treatment options include corticosteroids, immunosuppressants, and targeted therapies. The treatment of diffuse systemic sclerosis trial showed that high-dose D-penicillamine in early diffuse systemic sclerosis trial was not beneficial. Interstitial lung disease secondary to systemic sclerosis renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial showed that high-dose D-penicillamine was not beneficial compared to low-dose D-penicillamine.

Bronchiectasis in systemic sclerosis is a common manifestation and can be managed with bronchodilators, antibiotics, and lung volume reduction surgery. Pulmonary hypertension is another common manifestation in systemic sclerosis and can be managed with endothelin receptor antagonists. Induction of therapy include early disease, evidence of skin involvement or autoantibody status.

In conclusion, the management of interstitial lung disease in systemic sclerosis is challenging and requires a multidisciplinary approach. The use of targeted therapies, such as bosentan, may improve outcomes in selected patients. The role of corticosteroids remains unclear, but their use is often avoided due to side effects.

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trend toward improved FVC in the cyclophosphamide group but this did not achieve statistical significance\(^\text{35}\). Thus, it remains unclear what the true role of IV cyclophosphamide 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\(^\text{36-38}\). It is currently being studied in the Scleroderma Lung Study II as a possible alternative to cyclophosphamide for the treatment of ILD associated with SSc and represents an attractive less toxic therapy to cyclophosphamide if proven to be effective.

**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\(^\text{59}\) and occurs at low prednisone doses with a mean dose of only 7.4 mg in one series\(^\text{40}\). 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.

Endothelin receptor antagonists have been effective in the treatment of pulmonary hypertension associated with SSc. Bosentan for ILD was recently studied in a prospective, double-blind, randomized placebo-controlled, parallel group study. In the 163 patient study, the drug failed to demonstrate a difference in the primary endpoint of a change in six-minute walk distance. Secondary end points of time to death and worsening of PFTs were also no different\(^\text{41}\). This negative study mirrors negative results seen in trials of endothelin receptor antagonists in IPF\(^\text{42}\).

Imatanib is a tyrosine kinase inhibitor that is an attractive agent because of the role tyrosine kinases play in fibrosis\(^\text{33}\). In an open label trial of 24 patients, use of imatanib was associated with a statistically significant improvement in FVC, although this effect was more
pronounced in SSc patients without ILD. Imatinib is currently being further investigated for a possible role in SSc associated ILD and for SSc in general14.

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, cytoxan remains the best studied therapeutic agent although alternatives are actively being evaluated. The role of other immunosuppressive agents or other pathways remains undetermined and offer hope for future therapeutic interventions.

The Scleroderma Foundation thanks mary Beth Scholand, M.D., Elisabeth Carr, M.D. and Tracy Frech, M.D. for their assistance in the preparation of this brochure.

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Importance of ground-glass attenuation in chronic diffuse infiltrative lung disease:

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