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Lung Involvement in Systemic Sclerosis

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Summary

Scleroderma is a multisystem disease characterized by a severe inflammatory process and exuberant fibrosis. Lung involvement is a frequent complication and a leading cause of morbidity and mortality in this syndrome. Two major pulmonary syndromes are associated with scleroderma; a pulmonary vascular disorder evolving over time into relatively isolated pulmonary arterial hypertension (PAH), and interstitial lung disease (ILD). Each syndrome, when present, is a cause of morbidity and significantly reduces survival of scleroderma patients when compared to patients free of lung complication. When pulmonary hypertension and ILD are combined, survival is further reduced. Current therapy appears to have no meaningful effect on either condition and, thus, there is a need for better understanding of underlying pathogenic mechanisms. This review focuses on clinical, diagnostic, and therapeutic features of PAH and ILD as well as other frequent but less debilitating lung complications of scleroderma.

Scleroderma or systemic sclerosis (SSc) is a heterogeneous disorder characterized by endothelial dysfunction, dysregulation of fibroblasts resulting in excessive production of collagen, and profound abnormalities of the immune system1. These changes cause progressive fibrosis of the skin and internal organs, system failure and death. While the etiology of SSc is generally unknown, genetic and environmental factors are thought to contribute to host susceptibility2. SSc, whether presenting in the limited or diffuse form, is a systemic disease with the potential for multiple organ system involvement including the gastrointestinal, cardiac, renal, and pulmonary systems3. Pulmonary manifestations of SSc include, but are not limited to, pulmonary vascular diseases such as pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease (PVOD), interstitial lung disease (ILD), and increased susceptibility to lung neoplasms. The emphasis of this review will be on ILD and PAH since these two syndromes are by far the most common lung manifestations and leading causes of death in SSc.

1 Incidence and Prevalence of Systemic Sclerosis

Estimates of incidence and prevalence of systemic sclerosis have varied widely by the period of observation, disease definition, and population under study4. Although the incidence of SSc seemed to be increasing in the middle part of the last century, the rate of

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occurrence has stabilized after the widespread use of a standard classification system5. However, there continues to be marked geographic variation in the occurrence of the disease, supporting a role for environmental factors in disease pathogenesis. Prevalence of SSc ranges from 30-70 cases per million in Europe and Japan6-8 to ~240 cases per million in the United States (US) [5]. Incidence varies similarly by geographic area, with the highest rates found in the US (~19 persons per million per year)4.

2 Pulmonary Vascular Involvement

2.1 Scleroderma-Associated Pulmonary Arterial Hypertension

Pulmonary hypertension, defined as a mean pulmonary arterial pressure greater than 25 mm Hg, is a cause of significant morbidity and mortality9-11 and can be isolated in SSc, occurring as PAH (SSc-associated PAH or SSc-PAH), or in combination with ILD [pulmonary hypertension (PH)-ILD]. It has become clearer over the past few years that these two entities (SSc-PAH and PH-ILD) carry a very different prognosis in patients with SSc and will, therefore, be reviewed separately.

PAH, hemodynamically defined as mean pulmonary arterial pressure greater than 25 mmHg with a pulmonary capillary wedge pressure equal or less than 15 mmHg[12], is characterized by increased pulmonary vascular resistance due to remodeling and occlusion of the pulmonary arterioles. Left untreated, PAH leads irremediably to right ventricular (RV) hypertrophy, pressure overload and dilation resulting in death, generally from RV failure, within 2-3 years of the initial diagnosis[9]. It has been increasingly appreciated that the integrity of the RV function, rather than the degree of pulmonary vascular injury, is the major determinant of symptoms and mortality in patients with PAH9, 13. In fact, RV dysfunction at time of presentation, as reflected by an elevation in right atrial pressure, the presence of pericardial effusion or depressed cardiac output, is by far the best prognosticator of death9.

2.1.1 Prevalence of Scleroderma-Associated Pulmonary Arterial Hypertension

—Estimates of the prevalence of PAH in patients with SSc have varied widely based on the definition of pulmonary hypertension and the method of obtaining the measurements (*i.e.*, echocardiography or cardiac catheterization). Using echocardiography as the diagnostic tool, prevalence of pulmonary hypertension in SSc have been overestimated, ranging between 35-49%14, [15]. For example, in a study of 709 consecutive patients who underwent echocardiography, the prevalence of pulmonary hypertension (defined as RV systolic pressure > 35 mm Hg) was 38%[16]. However, relying on cardiac catheterization as gold standard for diagnosis, more recent prospective studies have shown that the prevalence of pulmonary hypertension is indeed between 8 and 12%17, 18, a more conservative and accurate figure regarding this complication. In all patients with SSc, PAH significantly worsens survival and is, after ILD, the leading cause of mortality in these patients5, 19, 20. Assuming a conservative 10% estimate of PAH prevalence among patients with SSc in the United States, SSc-PAH may affect as many as 24 individuals per million and thus be more common than other forms of PAH in the World Health Organization (WHO) group 1, including IPAH[10]. Yet in a large French PAH registry, connective tissue disease (mainly represented by SSc) accounts for only 15% of PAH cases (as opposed to 40% for IPAH) referred to pulmonary vascular centers21, suggesting that patients with SSc-PAH may be underdiagnosed or referral to specialized centers for diagnosis and treatment may be limited. In a prospective multicenter study, also from France, in which SSc patients with no evidence of PAH at baseline were followed for a mean duration of 41 ± 5 months, the incidence of PAH was estimated at 0.61 cases per 100-patient-years18.

2.1.2 Clinical features—Risk factors for the development of PAH in SSc patients have traditionally included late-onset disease16 although a recent study suggests that early-onset PAH occurs in approximately half of SSc patients22. Additional risk factors include an isolated reduction in Diffusing lung capacity to carbon monoxide (DLCO), an Forced vital capacity (FVC)/DLCO ratio greater than 1.623, 24, or a combined decreased DLCO/alveolar volume with elevation of serum N-terminal pro-brain natriuretic peptide (N-TproBNP) levels25, and female gender23 with post-menopausal onset of disease26 (Box 1). Other factors include the severity[24] and duration[27] of Raynaud phenomenon, digital ulceration[24, 28], multiple telangiectasiae[28, 29], and reduced nailfold capillary density[28, 30].

Box 1: Risk Factors for Development of Pulmonary Arterial Hypertension in Systemic Sclerosis

(**DLCO**: Diffusing lung capacity to carbon monoxide; **FVC**: Forced vital capacity; **N-TproBNP**: N-terminal brain natriuretic peptide)

Limited Systemic Sclerosis[24]

Late age of onset[16]

Postmenopausal onset[26]

Raynaud's phenomenon[24, 27]

Digital ulcerations[24, 28]

Multiple telangectasiae[28, 29]

Reduced nailfold capillary density[28, 30]

↓ DLCO[23, 164]

FVC%/DLCO% > 1.6[164]

↑ NT-pro BNP serum level[25]

Antibodies (e.g., anti-U3 RNP) [111]

Typically, patients with SSc-PAH are predominantly women, have limited SSc, are older and have seemingly less severe hemodynamic impairment compared to IPAH patients[31]. Like in IPAH, clinical symptoms are non specific, including dyspnea, and functional limitation which may be more severe than in IPAH due not only to older age but also to frequent involvement of the musculoskeletal system in these patients. SSc-PAH patients also tend to have other organ involvement such as renal dysfunction and intrinsic heart disease. Indeed patients with SSc (even in the absence of PAH) tend to have depressed RV function32, 33 and left ventricular systolic as well as diastolic dysfunction34. Like IPAH patients, SSc-PAH patients have severe RV dysfunction at time of presentation but have more severely depressed RV contractility compared to IPAH patients35. In addition, SSc-PAH patients tend to have more commonly LV diastolic dysfunction and a high prevalence of pericardial effusion (34% compared to 13% for IPAH)[31]. In both groups, pericardial effusion portends a particularly poor prognosis31. SSc-PAH patients also tend to have more severe hormonal and metabolic dysfunction such as high levels of N-TproBNP36, 37 and hyponatremia38. Both N-TproBNP and hyponatremia have been shown at baseline36-38, and with serial changes (for N-TproBNP36), to correlate with survival in PAH.

2.1.3 Early Detection—An algorithm for detection of PAH in patients with SSc may be helpful if based on a combination of symptoms and screening echocardiography (Figure 1). In a large French study, patients with SSc with tricuspid regurgitation velocity (TRV) jet by

transthoracic echocardiography greater than 3 m/sec, or between 2.5 and 3 m/sec if accompanied by unexplained dyspnea, were systematically referred for right heart catheterization18. This approach allowed to detect incident cases of SSc-PAH with less severe disease (as judged on hemodynamic data) compared to patients with known disease. Therefore, unexplained dyspnea should prompt a search for PAH in these patients, in particular in the setting of a low single breath DLCO or declining DLCO over time24, echocardiographic findings suggestive of the disease (elevated TRV jet or dilated RV or atrium), or elevated levels of N-TproBNP which can reflect cardiac dysfunction and have been found to predict the presence of SSc-PAH36. Thus, systematic screening might allow detection of early disease and prompt therapy which is theoretically beneficial from a prognostic standpoint39.

2.1.4 The Problem of Pulmonary Veno-Occlusive Disease in SSc-PAH— Pulmonary venoocclusive disease (PVOD) is a syndrome characterized by intimal proliferation and fibrosis of the intrapulmonary veins and venules in addition to some involvement of the arteriolar bed40. A definite diagnosis is usually obtained by biopsy of the lung41, which is however risky in PAH. Alternatively, the diagnosis can be suggested clinically. PVOD appears to be an underrecognized entity in SSc-PAH41, which poses a conundrum considering the known risk of pulmonary edema with the use of vasodilators in this condition41. Compared with PAH, PVOD affects more male than female patients, and is characterized by higher prevalence of tobacco abuse, lower DLCO, lower arterial oxygen tension at rest and more pronounced oxygen desaturation with exercise. High-resolution computed tomography of the chest (HRCT) typically demonstrates centrilobular groundglass opacities, septal lines, and lymph node enlargement41. Two recent histological studies have underlined the more frequent involvement of pulmonary veins than previously recognized in SSc-PAH, perhaps explaining in part why these patients are often refractory to specific PAH treatment as compared with IPAH patients40, 42 and inclined to develop pulmonary edema in response to vasodilators. However, a recent retrospective analysis indicates that epoprostenol, if given at small incremental levels along with high dose diuretics, can improve clinical (e.g., functional class) and hemodynamic (e.g., cardiac index and pulmonary vascular resistance) parameters and might be a reasonable bridge to urgent lung transplantation for PVOD patients43. Ultimately, lung transplantation remains the most suitable alternative for PVOD and should be promptly considered once the diagnosis is firmly established.

2.1.5 Therapy for SSc-PAH—Recognizing that one-year survival rates for SSc-PAH patients range from 50-87%[17, 19, 31, 44-46], which are considerably lower than the 88% one year survival for IPAH patients[47], the current challenge for the PAH community is to develop improved therapies specifically targeted for these patients.

Evidence of chronically impaired endothelial function[48-50], affecting vascular tone and remodeling, has been the basis for current therapy of PAH. Vasodilator therapy using high dose calcium channel blockers is an effective long-term therapy51, but only for a minority of patients (e.g., less than 7%[52] of IPAH patients) who demonstrate acute vasodilation (*e.g.*, to NO or adenosine) during hemodynamic testing, and an even smaller number of patients with SSc-PAH. Indeed, the vast majority of SSc-PAH patients fail to show a vasodilator response to acute testing[21]. Therefore, high dose calcium channel therapy is usually not indicated for patients with SSc-PAH although most patients often receive these drugs at low dosage, typically for Raynaud's syndrome.

2.1.5.1 Anti-inflammatory drugs: It has been increasingly recognized that inflammation may play a significant role in various types of pulmonary hypertension[53], including IPAH and PAH associated with connective tissue diseases (CTD, including SSc) and human

immunodeficiency virus infection. Interestingly, occasional patients with severe PAH associated with some forms of CTD (such as systemic lupus erythematosus, primary Sjögren syndrome, and mixed CTD) have had dramatic improvement of their pulmonary vascular disease with corticosteroids and/or immunosuppressive therapy[54], emphasizing the relevance of inflammation in these subsets of patients. However, this type of dramatic response is generally not observed in patients with SSc-PAH whose disease is usually quite refractory to immunosuppressive drugs54.

2.1.5.2 Prostaglandins: Prostacyclin (e.g., epoprostenol) has potent pulmonary vasodilator but also anti-platelet aggregating and antiproliferative properties55, and has proven effective in improving the exercise capacity, cardiopulmonary hemodynamics, WHO functional class (WHO FC), symptoms, as well as survival in patients with PAH when given by continuous infusion56-58. Although there have been no randomized trials using this agent to assess long-term effect on survival, analysis of cohorts of patients on continuous intravenous epoprostenol compared with historical control groups (a questionable comparison for many obvious reasons) demonstrated clear benefits in survival in patients with WHO FC III and IV47, 59. Initially proposed as a bridge to lung transplantation, intravenous epoprostenol is now considered as first-line therapy in severe PAH (WHO FC IV) and in some patients an alternative to lung transplantation60.

Treprostinil, a prostacyclin analogue suitable for continuous subcutaneous administration, has been shown to have modest effects on symptoms and hemodynamics in PAH[61]. In a small study of 16 patients (among whom 6 had CTD related PAH), intravenous treprostinil was shown to improve hemodynamics 6 minute walk distance (6MWD), FC, and hemodynamics after 12 weeks of therapy[62]. Although the safety profile of this drug is similar to IV epoprostenol, required maintenance doses are usually twice as high compared to epoprostenol. However, for patients with SSc-PAH, the lack of requirement for ice packing and less frequent mixing of the drug offer significant advantages considering these patients' sensitivity to cold exposure. In summary, both epoprostenol and treprostinil are FDA approved for PAH, but are cumbersome therapies requiring continuous parenteral administration with potential numerous adverse and severe side effects (*e.g.*, infection and possibility of pump failure63), which make these drugs less than ideal.

In SSc-PAH, continuous intravenous epoprostenol improves exercise capacity and hemodynamics[64], compared to conventional therapy, however there has been no demonstrable effect on survival. Badesch et al recently demonstrated long-term survival (47% survival rate at 3 years) for SSc-PAH patients treated with intravenous epoprostenol[65] suggesting that this is an adequate form of therapy for these patients, although the results are not significantly different form oral medical therapy for these patients44, 66. In addition, several reports of pulmonary edema in SSc-PAH patients treated with prostaglandin derivatives, both in acute and chronic settings, have raised the suspicion of increased prevalence of PVOD in these patients40, [67, 68], and concern about usefulness of these drugs for this entity. Furthermore, considering the frequent digital problems and disabilities that these patients often experience, this form of therapy can be quite challenging and may increase the already heavy burden of disease. Nevertheless, intravenous prostaglandin therapy remains a valuable therapeutic option for patients with SSc-PAH with WHO FC IV, and in FC III patients who demonstrate no improvement on oral therapy.

2.1.5.3 Endothelin receptor antagonists: Randomized, placebo-controlled trials of 12-16 weeks duration demonstrated a beneficial effect of bosentan therapy on functional class, 6MWD, time to clinical worsening and hemodynamics in PAH69, 70. In these studies, roughly one fifth of the population consisted of SSc-PAH patients while a large majority had a diagnosis of IPAH. A subgroup analysis, performed by Rubin et al, reported a non-

significant trend towards a positive treatment effect on 6MWD among the SSc-PAH patients treated with bosentan compared to placebo[70]. At most, bosentan therapy prevented deterioration in these patients (as assessed by an increase of 3 m in the 6MWD in the treated group compared to a decrease of 40 m in the placebo group). This less than optimal effect of therapy in patients with SSc-PAH is unclear but may be related to the severity of PAH at time of presentation, as well as other factors such as, hypothetically, more severe RV and pulmonary vascular dysfunction, as compared to patients with other forms of PAH (*e.g.*, IPAH).

In a recent analysis of patients with PAH associated with CTD (*e.g.*, patients with lupus, overlap syndrome, and other rheumatological disorders) included in randomized clinical trials of bosentan, there was a trend toward improvement in 6MWD and improved survival compared to historical cohorts[71]. Our experience suggests that long-tem outcome of first-line bosentan monotherapy is inferior in SSc-PAH compared to IPAH patients, with no change in functional class and worse survival in the former group[72].

In an effort to target the vasoconstrictive effects of endothelin while preserving its vasodilatory action, selective endothelin-A receptor antagonists have been developed. Sitaxsentan, which is only approved in Europe for treatment of PAH, improved exercise capacity (*i.e.*, change in peak VO_2 at week 12, which was the main end-point of the study)73. Elevation in liver enzymes were noted in 10% of patients at the higher dose tested (300 mgs orally once daily). Patients with PAH associated with CTD represented 24% of the study group. A post-hoc analysis of 42 patients (33 patients who received the drug and 9 patients who received placebo) with CTD-PAH demonstrated improved exercise capacity, quality of life, and hemodynamics with sitaxsentan although elevated liver enzymes were reported in 2 patients74. A large pacebo-controlled, randomized trial of ambrisentan, the only currently FDA-approved selective endothelin receptor antagonist, improved 6MWD in PAH patients at week 12 of treatment, however, the effect was larger in patients with IPAH compared to patients with CTD-PAH (range of 50-60 meters versus 15-23 meters, respectively)75. Ambrisentan is generally well tolerated although peripheral edema (in up to 20% of patients75) and congestive heart failure have been reported.

2.1.5.4 Phosphodiesterase inhibitors: Sildenafil, a phosphodiesterase type V inhibitor that reduces the catabolism of cGMP, thereby enhancing the cellular effects mediated by nitric oxide, has become a widely used and highly efficacious therapy for PAH. The SUPER trial showed that sildenafil therapy led to an improvement in the 6 MWD in patients with IPAH and PAH related to CTD or repaired congenital heart disease (patients were predominantly functional class II or III) at all three doses tested (20, 40, and 80 mgs, given three times a day). Since there were no significant differences in clinical effects and time to clinical worsening at week 12 between the doses, the FDA recommended a dose of 20 mgs three times a day. In a post-hoc subgroup analysis of 84 patients with PAH related to CTD (forty-five percent of whom had SSc-PAH), data from the SUPER study suggest that sildenafil at a dose of 20 mgs improved exercise capacity (6MWD), hemodynamic measures and functional class after 12 weeks of therapy[76]. However, for reasons that remain unclear (but in part related to the limitations of that study such as post-hoc subgroup analysis), there was no effect for the dose of 80 mgs three times a day on hemodynamics in this subgroup of patients with CTD-related PAH. For this reason and because of the potential of increased side-effects (such as bleeding from arterio-venous malformations common in these patients) at high doses, we have opted at our center for sildenafil dosage of 20 mgs three times a day for our SSc-PAH patients as standard therapy. Higher doses are occasionally attempted in case of limited response. At this time, because of its favorable safety profile, oral sildenafil is our drug of choice for first line oral therapy for SSc-PAH patients with FC II or III. The impact of long-term sildenafil therapy on survival in patients with SSc-PAH remains to be

determined. Finally, tadalafil, another phosphodiesterase inhibitor, has now been shown to be effective for PAH77 although subgroup analysis has not been performed yet and thus its effects on SSc-PAH remain unclear. Tadalafil has the advantage over sildenafil of single daily dosage.

2.1.5.5 Tyrosine kinase inhibitors: The finding that there is pathologically aberrant proliferation of endothelial and smooth muscle cells in PAH[78], as well as increased expression of secreted growth factors such as VEGF and bFGF, has caused a shift in paradigm in treatment strategies for this disease. Some investigators have likened this condition to a neoplastic process reminiscent of advanced solid tumors[79]. As a result, anti-neoplastic drugs have been tested in experimental models80, 81 and some occasional patient case reports82-84. Two strategies are currently tested for treatment of PAH: disruption of PDGF and VEGF signaling pathways. STI-571/imatinib (Gleevec®/Glivec®), originally developed specifically to inhibit the Bcr-Abl kinase, is the prototypical PDGFR signaling inhibitor currently under investigation85. This and sorafenib (Nexavar®), the second drug currently being tested in PAH, are FDA-approved for other conditions (such as gastrointestinal malignancies and renal and hepatocellular carcinomas) and their efficacy is attributed to their dual inhibition of VEGF and PDGF signaling pathways. Based on evidence that PDGF signaling is an important process in the pathophysiology of PAH86, imatinib has been tested and shown to be effective in experimental models of PAH80. The results of a phase II multicenter trial to evaluate the safety, tolerability, and efficacy of this drug in patients with PAH have recently published and indicate that imitanib is well tolerated in PAH patients. While there was no significant change in 6 minute walk distance (primary end-point) there was a significant decrease in pulmonary vascular resistance and an increase in cardiac output in imatinib-treated patients versus placebo87. Whether these new anti-neoplastic drugs with anti-tyrosine kinase activity will have a role in SSc (where there is evidence for both dysregulated proliferation and increased expression of growth factors such as VEGF88) or in IPAH remains to be determined. Interestingly, a single case report suggests significant improvement of right ventricular function with imatinib treatment in a SSc-PAH patient. Also of note is that imatinib is being investigated for SSc-related interstitial lung disease89.

2.1.5.6 Combined therapy: It is now common practice in various pulmonary hypertension centers to add drugs when patients fail to improve on monotherapy. Adding inhaled iloprost to patients receiving bosentan has been shown to be beneficial in a small, randomized trial90. Combining inhaled iloprost with sildenafil is mechanistically appealing and anecdotally efficacious as these drugs target separate, potentially synergistic pathways90, 91. Several multicenter trials are now exploring the efficacy of various combinations of two oral drugs or one oral and one inhaled drug. The results of the PACES trial demonstrate that adding sildenafil (at a dose of 80 mgs three times a day) to intravenous epoprostenol improves exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life92. About 21% of these patients had CTD, including 11% with SSc-PAH. Although no specific subgroup analysis is provided, improvement was apparently mainly in patients with IPAH and limited to patients who had relatively better exercise function at baseline. We reported our experience of adding sildenafil to patients with IPAH or SSc-PAH after they failed initial monotherapy with bosentan93. While the combination improved the 6MWD and FC in IPAH patients, the outcome in patients with SSc-PAH was less favorable, but may have halted clinical deterioration. In addition, there were more side-effects reported in the SSc-PAH compared to the IPAH patients, including hepatotoxicity that developed after addition of sildenafil to bosentan monotherapy93. Sildenafil and bosentan are substrates of the CYP 3A4 cytochrome, and combination therapy leads to significant increases in bosentan serum levels, and significant decreases in sildenafil concentration (since bosentan induces CYP 3A4)94. The clinical significance of these findings is unclear

at this time, and these two drugs are often used in combination in clinical practice without obvious untoward effects.

2.1.5.7 Anticoagulation: The rationale for the use of anticoagulation in severe PAH is based on pathologic evidence of pulmonary thromboembolic arterial disease and thrombosis *in situ* in patients with IPAH95, and two clinical studies (a retrospective analysis96 and a small, non-randomized prospective study51) demonstrating a significant beneficial effect of anticoagulation on survival in IPAH. In the former study, survival was significantly prolonged for patients who received long-term on anticoagulation, as compared with those who were not treated with warfarin96. In a study primarily aimed at assessing the effects of high dose calcium channel blockers on IPAH, improved survival with oral anticoagulation was demonstrated *a posteriori* irrespective of vasodilator use[51]. Based essentially on the findings of these two studies, anticoagulation is routinely recommended in the treatment of IPAH patients. The role of anticoagulation in other forms of PAH, in particular in SSc-PAH or other forms of CTD is less clear. Theoretically, there is potential for increased bleeding in patients with CTD, particularly with SSc where gastro-intestinal telangiectasias may be common. Our experience with anticoagulation in over 100 patients with SSc-PAH suggests that less than 50% of these patients remain on long-term anticoagulation therapy. The reason for discontinuing anticoagulation is often related to occult bleeding in the gastrointestinal tract from a source often difficult to diagnose in our experience.

2.1.5.8 Lung transplantation: Lung transplantation (LT) is typically offered as a last resort to patients with PAH who fail medical therapy. Although SSc is not an absolute contraindication to lung transplantation, patients with SSc often have associated morbidity and organ dysfunction other than the lung that place them at a specifically high risk for LT. The involvement of the esophagus with severe motility disorder and gastroesophageal reflux in patients with SSc is an example of specific risk that discourages surgeons from considering these patients because of the enhanced post-operative potential of aspiration and damage to the recipient lung. For these reasons, patients with SSc-PAH are often denied the LT option. However, if properly screened and approved for LT, patients with SSc experience similar rates of survival 2 years after the procedure compared with patients who receive LT for pulmonary fibrosis or IPAH[97]. A recent retrospective study suggests that 1-year survival rate is no different for SSc patients (transplanted for respiratory failure related to PAH or interstitial lung disease) compared to patients with IPF although acute rejection appears to be more common for the former group98.

2.1.6 Survival of patients with SSc-PAH—While there has been a recent significant increase in the number of drugs targeting specific pathways in PAH99, survival of patients with SSc-PAH on modern therapy remains unacceptably low despite recent claims of improvement compared to similar historical controls[39]. The reason for a discrepancy in survival between IPAH and SSc-PAH patients remains poorly understood and may involve complex pathogenic alterations affecting not only the proximal and distal pulmonary vessels but also the heart (such as inflammatory myocarditis). A recent study focused on SSc-PAH suggests that specific components of right ventricular dysfunction, as well as renal impairment (probably as a mere consequence of severe cardiac dysfunction and neuroendocrine activation), contribute significantly to increased mortality in SSc-PAH patients[44]. Thus, a better understanding of the underlying pathophysiology of pulmonary vascular and cardiac remodeling, as well as RV-pulmonary vascular coupling in this disease, is needed for better targeted therapy100. Whether specific anti-inflammatory agents or drugs targeting tyrosine kinase activity hold any promise of enhanced response is unclear at this time but needs to be further explored.

2.1.7 Specific Challenges Related to SSc-PAH—Several issues have substantially limited progress in the diagnosis and management of SSc-PAH. First, currently available outcome measures, including the 6-minute walk test and invasive or non-invasive cardiopulmonary hemodynamics, provide global assessments of function. They do not allow dissection or consideration of the components of the cardiovascular response, in particular RV function, proximal and distal vascular remodeling, and the interaction between the pulmonary vasculature and the RV, which may be particularly important in patients with SSc-PAH[100]. Furthermore, while some progress has been made in understanding the genetics of IPAH with the discovery of specific mutations in the bone morphogenesis protein receptor (BMPR2)[101], 102, little is known about genetic and/or phenotypic characteristics that might predict the development of PAH, RV-PV dysfunction, response to therapy, and survival in patients with SSc-PAH. Finally, delay in diagnosis and referral to specialized centers for treatment of PAH may be a contributing factor to poor prognosis in these patients.

In summary, SSc-PAH is a common cause of pulmonary hypertension but has significantly worse outcome compared to other diseases, such as IPAH, within group 1 of the WHO classification. In addition, modern therapy for PAH appears to be of limited value in SSc-PAH. Similarly, currently available markers of disease severity or response to therapy in SSc-PAH are either limited or lacking. Therefore, there is an urgent need to identify potential genetic causes and novel physiologic and imaging biomarkers that will allow a better understanding of the underlying pathogenesis and serve as reliable tools to monitor therapy in this devastating syndrome.

3 Lung Parenchymal Involvement

Most patients with SSc have some degree of lung parenchymal involvement in the form of interstitial thickening and fibrosis which, when extensive may be clinically significant. Interstitial lung disease (ILD) is the most common pulmonary manifestation of SSc, affecting about 40% of patients, and by far the leading cause of morbidity and mortality20. ILD most often complicates the diffuse cutaneous form of SSc103-105 but can also be associated with the limited form of the disease or with SSc without cutaneous involvement (SSc sine scleroderma)106. In addition, there is no correlation between the extent and severity of the skin disease and pulmonary parenchymal involvement107. ILD was found to be associated with African-American ethnicity, high skin score, elevated serum CPK, hypothyroidism, and cardiac involvement in a large cohort of SSc patients108.

3.1 Diagnosis

The development of ILD in patients with SSc may be slow and progressive. The patients may remain asymptomatic despite the presence of physical findings such as crackles on auscultation or interstitial thickening on chest radiography. The symptoms are non specific and most commonly include dyspnea on exertion, a dry cough or fatigue. Chest discomfort or pain and hemoptysis are uncommon. Physical examination will most typically reveal bilateral inspiratory and expiratory crackles (so called “Velcro” crackles) on auscultation of the lung bases. Serum serology may reveal the presence of antitopoisomerase I/Scl-70, anti-U3RNP, Th/To, and antihistone autoantibodies at presentation and thus may identify SSc patients at high risk for developing ILD[109-113]. However, anti-topoisomerase/Scl-70 has generally limited sensitivity for diagnosis of ILD in SSc patients114. Anticentromere antibodies are unusual in this syndrome115.

Alterations in pulmonary function tests often precede symptoms or changes in chest radiography. However, early ILD cannot be excluded by normal spirometry. A reduction in single breath DLCO appears to be one of the earliest detectable functional correlates of lung

disease in SSc-ILD[105] and is present in over 70 % of patients. A decrease in DLCO correlates with the severity of ILD detected by high resolution computed tomography (HRCT) and predicts poor outcome[116]. On the other hand, plain chest radiography is rather insensitive for detecting early ILD. HRCT changes suggestive of ILD include ill-defined, subpleural infiltrates or densities in the posterior segments of the lower lobes, interstitial reticular infiltrates and subpleural honeycombing changes. Traction bronchiectasis and large cystic changes develop with progressive disease114, 117. The extent of pulmonary fibrosis as assessed on HRCT is negatively correlated with FVC on spirometry and is a powerful predictor of survival118. Since SSc-ILD is predominantly subpleural, histological changes are more likely to be found in peripheral lung biopsy compared to other lung locations[105]. Histological findings correlate relatively well with HRCT findings[119].

However, the diagnosis of SSc-ILD is frequently suggested by the constellation of symptoms, physical findings, pulmonary function and HRCT abnormalities. Thus lung biopsies (e.g., video-assisted thoracoscopic biopsies) are seldom needed except for ruling out other parenchymal processes[116-118, 120, 121].

In a large study of patients with early symptomatic SSc-ILD, almost half of the patients presented with ground-glass opacification[122], which correlated with increased numbers of inflammatory cells in the bronchoalveolar lavage (BAL) fluid. On the other hand, a reticular HRCT pattern is more often associated with changes consistent with a histological diagnosis of usual interstitial pneumonitis (UIP)114, 119, 123, 124. The severity of lung involvement (defined by HRCT) also correlates with the type of inflammatory cells obtained by BAL: excess lymphocytes may be present when radiological changes are minimal while excess eosinophils are associated with early disease and neutrophils with more extensive disease125, supporting the notion that specific inflammatory cells are involved at different stages of SSc-ILD. While patients with SSc-ILD typically have elevated numbers of neutrophils, eosinophils, and lymphocytes, and occasionally mast cells126, performance of BAL for diagnosis is not routinely mandated. However, the presence of greater than 3 percent neutrophils and/or greater than 1 percent eosinophils in BAL fluid is usually indicative of active alveolitis, and may prompt initiation of immunosuppressive therapy127 although recent data indicate that such treatment may not offer any specific advantage (as assessed by changes in FVC) when comparing patients with and without evidence of alveolitis128.

3.2 The impact of gastroesophageal reflux

Impaired esophageal motility and gastroesophageal reflux are common in SSc and may cause recurrent aspiration of gastric content129. Investigators have analyzed the correlation between esophageal dysmotility and the presence of ILD as assessed by pulmonary function testing and HRCT130-132 (124-126). Presence of severe esophageal motor impairment was found to be associated with significantly decreased values of DLCO and evidence of ILD by HRCT. Furthermore, a 2-year follow-up suggested that patients with severe esophageal dysmotility had greater deterioration in DLCO and increased frequency of ILD by HRCT[130]. The association between esophageal dysmotility and ILD, however, has not always been corroborated132 and, thus, the exact role of esophageal reflux in the pathogenesis of SSc-ILD remains unclear.

3.3 Prognosis

SSc-ILD portends a poor prognosis with increased mortality[116, 133-135]. In a retrospective study of 953 SSc patients, SSc-ILD patients with severe ILD had a 30% survival rate at 9 years, versus 72% survival rate in patients without major organ involvement[135]. The most

rapid decline in FVC occurred within the initial three years of disease onset, suggesting that lung injury and fibrosis may be relatively early complications.

The prognostic value of BAL is of unclear value[116, 126, 136, 137], with one retrospective study suggesting that increased eosinophils in the BAL fluid is associated with a poor prognosis while a larger prospective cohort study of 141 patients with SSc-ILD demonstrating that BAL eosinophils did not correlate with mortality, rate of functional deterioration, or progression-free survival116, [136]. Increased neutrophils in BAL fluid was associated with more extensive lung disease on HRCT, a greater reduction in DLCO, and early mortality (HR 8.40, 95% CI 1.91-36.95), but did not predict the rate of functional deterioration or progression-free survival[136]. As mentioned above, a prospective clinical trial of 158 patients with early-stage SSc and symptomatic lung involvement found that the presence or absence of neutrophils in BAL fluid had no bearing on the rate of worsening or response to therapy138.

Similarly, the prognostic value of lung biopsy in patients with SSc-associated ILD is of limited value whereas assessment of clinical severity and lung function impairment are better predictors of outcome. In a retrospective histopathological evaluation of 80 patients with biopsy proven SSc-ILD, 76 % had non-specific interstitial pneumonitis (NSIP) and 11 % had UIP[116], with fairly similar five-year survival rates of 82 and 91 %, respectively. Markers of a poor outcome in this study included low DLCO and a rapid decline of DLCO over three years116.

3.4 Treatment

It is thought that SSc-ILD, like other forms of ILD, results from an initial parenchymal lung injury of yet undefined mechanism, and characterized by significant inflammation followed by dysfunctional repair and exuberant fibrosis. Thus targeting inflammation is appealing since the initial insult likely remains unrecognized and the fibrotic stage is irreversible. However, the potential (and currently small) benefits of therapy must be weighed against the risks of potentially toxic drugs. Therapy may be initiated in patients who have early respiratory symptoms in the context of pulmonary function impairment and radiographic changes in particular if the latter are suggestive of early and active disease such as ground glass infiltrates or recent progression of infiltrates on HRCT.

3.4.1 Immunosuppressive agents—With multiple uncontrolled case series reporting clinical[139, 140], functional[139-147], and radiographic139, 142, 143 improvement in SSc-ILD patients treated with immunosuppressive agents, two prospective studies were recently completed. In a double-blind multicenter trial (Scleroderma Lung Study) of 158 patients with early SSc-ILD, dyspnea, and evidence of active alveolitis randomly assigned to receiving oral cyclophosphamide (≤2 mg/kg) or placebo daily for one year138, oral daily cyclophosphamide had modest clinical efficacy (a small but significant difference in FVC percent predicted between treatment and placebo) which raised optimism but prompted cautionary advice regarding the use of this toxic drug for these patients148. This is particularly relevant in light of a follow-up study reporting that the initial improvement in FVC138 persisted for 6 month after discontinuing cyclophosphamide therapy but was found insignificant at 24 month follow-up128 although improvement in respiratory symptoms and skin changes persisted. In a second prospective trial comparing monthly infusion of cyclophosphamide combined with prednisolone (20 mg on alternate days) followed by azathioprine versus placebo149, there was only an insignificant trend toward improvement in FVC (primary outcome) in the treatment group. There was, however, no significant improvement in DLCO or dyspnea. The treatment was felt to be well tolerated (no significant side-effects) and, at best, to stabilize pulmonary function tests. Since many

studies evaluating the efficacy of cyclophosphamide in SSc-ILD have used low dose glucocorticoid therapy[138, 145, 149], and since there is a high risk of SSc renal crisis in these patients, low dose glucocorticoid (~ 10 mg/day of prednisone) is usually recommended with cyclophosphamide.

Azathioprine has also been used for the treatment of SSc-ILD although with less success compared to cyclophosphamide[150], as suggested by a non blinded trial comparing these two drugs given in addition to low dose corticosteroids. FVC and DLCO seemed to remain stable in the cyclophosphamide group while these values declined in the azathioprine group. Adverse effects such as leukopenia were more frequent in the cyclophosphamide group. Preliminary data suggest that azathioprine may have a role as maintenance therapy in patients who have completed a course of cyclophosphamide. A retrospective series of 20 patients with SSc-ILD demonstrated stabilization or improvement in pulmonary function tests after a combination of six months of monthly intravenous cyclophosphamide followed by 18 months of azathioprine[151].

More recent experience with the use of mycophenolate mofetil, an inhibitor of lymphocyte proliferation, suggests potential effectiveness for this drug in treatment of SSc-ILD[152-154], with either improvement or stabilization of pulmonary function[155, 156]. The results of larger, randomized and controlled trials are needed before any conclusions and recommendations regarding this form of therapy can be drawn.

Imatinib mesylate, a tyrosine kinase inhibitor which has revolutionized the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, may be a highly promising therapy for various forms of fibrotic diseases[157, 158] including complications of SSc such as SSc-ILD and SSc-PAH (*vide supra*). Results with this and other more selective tyrosine kinase inhibitors are anxiously awaited.

3.4.2 Hematopoietic stem cell transplantation—Immunoablative therapy followed by autologous hematopoietic stem cell transplantation is being increasingly advocated for the treatment of severe SSc. The rationale is to reset the dysregulated immune system by eradicating exuberantly active auto-immune effector T and B cells and to induce T regulatory response [159, 160]. While experience so far indicates significant and sustained improvement of skin thickening and stabilization of major organ dysfunction[161], it is unclear at this time whether this therapy will have any impact on lethal SSc complications such as SSc-ILD and SSc-PAH. Hematopoietic cell transplantation should be currently viewed as an experimental form of therapy with sound mechanistic basis.

3.4.3 Lung transplantation—Lung transplantation (LT) is an option for patients with severe SSc-ILD who are not responsive to pharmacologic interventions. Carefully selected SSc patients undergoing lung transplantation have acceptable morbidity and mortality comparable to patients undergoing LT for idiopathic pulmonary fibrosis as suggested by recent studies[97, 98, 162]. A retrospective survey of 47 patients with SSc (mean age 46 years) who underwent lung transplantation determined that single lung transplantation was more common than double lung transplantation (57 versus 43 percent)[163]. Fifteen percent of the patients died within 30 days following transplant, and 32 % died later. Late mortality was most commonly due to infection; other causes included respiratory failure, malignancy, and pulmonary hypertension. The one- and three-year survival rates were 68 and 46 %, respectively, which did not differ from patients who received lung transplants for other conditions. One-year survival rate after lung transplantation is similar for SSc compared to IPF patients although acute rejection is more common[98].

4 Combined Pulmonary Vascular and Parenchymal Disease in Systemic Sclerosis

Typically, patients with isolated PAH have limited SSc disease and develop PAH after a duration of 10-15 years24. In contrast, patients with diffuse SSc are at greater risk of developing ILD, usually in the first 5 years after diagnosis of SSc when the most rapid rate of decline in FVC is observed164. However, patients with SSc, with limited or diffuse disease, may present at any stage in the course of their disease with pulmonary hypertension, whether associated or not with ILD[165]. From a phenotypic standpoint, it is important to note that patients with isolated PAH (SSc-PAH, i.e., no ILD) belong to Group 1 (PAH), while patients with pulmonary hypertension and ILD (SSc-ILD-PH) fall into Group 3, of the pulmonary hypertension classification[166].

SSc patients with ILD alone have a median survival of 5-8 years167; however, the impact of combined pulmonary hypertension and ILD has not been well characterized. A study by Trad et al in which pulmonary hypertension was assessed by RHC suggests an increased mortality for patients with SSc-ILD-PH compared to ILD alone168. In a recent study by Mathai et al, where consecutive SSc patients with RHC confirmed pulmonary hypertension with or without ILD were analyzed169, survival was significantly worse in SSc-ILD-PH compared to patients with SSc-PAH (1-,2-, and 3-year survival of 82%, 46%, and 39% vs. 87%, 79%, and 64% respectively, log-rank $p<0.01$). In multivariable analysis, ILD was associated with a 5-fold increased risk of death169. In another study by Condliffe et al of patients with CTD, 3 year survival rate was 28% for SSc-ILD-PH patients, thus significantly worse compared to 47% survival rate in the group of patients with SSc-PAH66. Of note, only 3 patients with SSc-ILD-PH (the group with the worse prognosis) underwent transplantation, probably because of the perceived heightened risk for transplantation in this group. Since standard medical therapy fails to demonstrate any significant benefit for these patients, the authors wisely suggest that prompt referral for transplant assessment of suitable patients should be considered more aggressively in this group66. In summary, very little is known, aside from anecdotal reports170, regarding the efficacy of medical therapy for SSc-PH-ILD. This subset of patients is routinely excluded (and wisely so because of their particularly poor prognosis) from clinical trials of PAH therapies as well as trials investigating therapies for ILD. However, these patients clearly deserve more attention and more focused therapy trials considering their very grim natural history.

5 Other Lung Complications in Systemic Sclerosis

Aside from the common complications of pulmonary vasculopathy and ILD reviewed above, other less frequent pulmonary complications have been reported in SSc. An occasional obstructive ventilator defect has been observed in non smoker CTD (including SSc) patients[171]. Pleural effusions, perhaps related to serositis172, 173, and spontaneous pneumothorax174 have been reported, the latter often in association with subpleural blebs in the context of ILD.

Several large studies have found a high prevalence of lung cancer in SSc patients[175, 176]. These patients are typically female with underlying ILD. The histological types of malignancy include bronchoalveolar carcinomas and adenocarcinomas[177], tumors less likely to be associated with a history of cigarette smoking[178]. However, a recent large population-based cohort study has questioned the link between SSc and lung cancer[179].

Finally myopathy and myositis in the context of an overlap syndrome are not uncommon complications of SSc and may cause respiratory symptoms through respiratory muscle dysfunction[180].

6 Conclusion

Pulmonary complications are common in SSc and, in the case of SSc-ILD and SSc-PAH, the leading causes of death. However, dyspnea may have many causes in patients with SSc and its assessment requires a systematic approach including a thorough history, physical examination, and additional screening testing such as echocardiography and chest imaging. Treatment of the various pulmonary complications remains disappointing although many promising therapies are emerging. A better understanding of the pathophysiology of the disease, whether related to the vasculopathy or parenchymal involvement, is greatly needed and will allow more effective targeted therapy.

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Glossary

6MWT	6 minute walk test
6MWD	6 minute walk distance
CTD	Connective tissue disease
DLCO	Diffusing lung capacity to carbon monoxide
FC	Functional class
FGF	Fibroblast growth factor
FVC	Forced vital capacity
HRCT	High resolution computed tomography
ILD	Interstitial lung disease
IPAH	Idiopathic pulmonary arterial hypertension
IPF	Idiopathic pulmonary fibrosis

LT	Lung transplantation
N-TproBNP	N-terminal brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PVOD	Pulmonary veno-occlusive disease
RV	Right ventricle
SSc	Scleroderma
SSc-PAH	Scleroderma-related PAH
TRV	Tricuspid regurgitation velocity
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

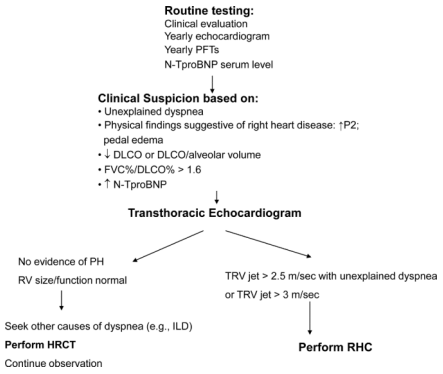

Figure 1. Algorithm for Detection of PAH in Patients with Scleroderma

Proposed algorithm for performance of routine clinical tests in patients with scleroderma which may allow early detection of pulmonary arterial hypertension or other causes of functional impairment such as cardiac dysfunction (e.g., left ventricular dysfunction) or parenchymal disease (e.g., IPF).

(DLCO: single breath diffusing capacity to carbon monoxide; FVC: forced vital capacity; HRCT-high resolution computed tomography; ILD: Interstitial lung disease; PFTs: Pulmonary function tests;;; RHC: right heart catheterization; RV: right ventricle; TRV: tricuspid regurgitation jet;).