REGULAR ARTICLE

Pulmonary Hypertension in Collagen Vascular Disorders: Systemic Sclerosis: An Overview of Systemic Sclerosis-Associated Pulmonary Hypertension

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Systemic sclerosis (SSc) is a disease state characterized by a significant lifetime risk for the development of pulmonary hypertension (PH). SSc-associated PH is comprised of a heterogenous array of phenotypes. SSc patients are at risk for both precapillary and postcapillary PH conditions. These include pulmonary arterial hypertension (PAH), PH secondary to interstitial lung disease (ILD-PH), and left heart disease associated PH. SSc-PAH is a vasculopathy that is distinct from idiopathic PAH and probably PAH associated with other connective tissue diseases. This concise review provides an overview of the various forms of SSc-PH, as well as advances in the screening, therapeutic management, and risk stratification strategies for the various types of SSc-PH. As the same SSc patient often displays multiple overlapping PH groups, treatment decisions are complex and often need to be individualized. This review also attempts to provide a rational framework for the management of SSc-PH patients with overlapping disease phenotypes.

INTRODUCTION

Systemic sclerosis (SSc) is a rare multisystemic connective tissue disease characterized by autoimmune dysregulation, chronic inflammation, and collagen deposition resulting in end-organ fibrosis.[1] There are 2 main phenotypes of SSc: diffuse cutaneous SSc (dc SSc) and limited cutaneous SSc (lc SSc), distinguished by the pattern and the extent of cutaneous involvement.[1] Diagnosis of SSc depends on the fulfillment of the 2013 American College of Rheumatology and European League Against Rheumatism classification criteria.[2] Morbidity and mortality in SSc are largely driven by end-organ dysfunction resulting from fibrosis and microvascular obliteration in the lungs, heart, and kidneys. Lung disease is the most common cause of death in the SSc population with interstitial lung disease (ILD) and pulmonary hypertension (PH) being the first and second leading causes of mortality, respectively.[1,3]

According to the Sixth World Symposium on Pulmonary Hypertension (WSPH), PH is classified into groups 1–5 based on the primary etiopathogenesis of the PH (Table 1).[4] SSc patients are at risk for multiple forms of PH.[5] While individual SSc patients can exhibit any one of the following phenotypes of PH, namely: groups 1, 1.6, 2, or 3; in clinical practice, there can be a considerable overlap in the expression of disease phenotypes. SSc-related pulmonary arterial hypertension (SSc-PAH) is the most common form of collagen vascular disorder-associated PAH in North America and Europe.[6,7] A rare subgroup of WSPH group 1 disease, or group 1.6, known as pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis (PVOD/PCH) has also been described in SSc patients.[5] SSc-related ILD is a leading cause of morbidity and mortality and WSPH group 3 PH has been reported in SSc-ILD patients (SSc-ILD-PH).[8] Finally, cardiac involvement in the form of myocardial fibrosis and myocardial dysfunction and associated WSPH group 2 PH (SSc-LVD-PH) have also previously been described in SSc patients.[9,10] This concise review aims to provide a brief overview of the epidemiology, screening, and description of the different phenotypes of SSc-PH, their pathophysiology and management.

Diagnosis and Epidemiology

In an SSc patient, the diagnosis of precapillary PH (WSPH groups 1, 1.6, and 3) is made using right heart catheterization (RHC) when the mean pulmonary artery pressure (mPAP) is >20 mmHg, pulmonary capillary wedge pressure (PCWP) is ≤15 mmHg, and the pulmonary vascular resistance (PVR) is ≥3 Woods Units, while a diagnosis of postcapillary PH (WSPH group 2) is made when PCWP is >15 mmHg in combination with similar criteria for mPAP.[11] Further characterization of the exact precapillary PH phenotype requires additional clinical data such as pulmonary function testing (PFT), chest imaging (high-resolution computed tomography [HRCT]), V/Q scan, and echocardiographic data.[4]

The prevalence of PH in individuals with SSc was noted to be around 7% from 1 European meta-analysis of 5 different studies. In this study, 83 out of 1165 individuals with SSc had PH with 77% (51% SSc-PAH, 26% SSc-ILD-PH) having precapillary PH, 21%

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postcapillary disease, while 2% had PVOD.[7] In the DETECT study, which included 62 participating centers from North America, Europe, and Asia, using a strategy to enrich for SSc-PAH (SSc duration > 3 years and diffusion capacity of the lung for carbon monoxide [DLCO] < 60% predicted), 145/646 screened patients, or 31% were found to have PH. SSc-PAH (WSPH Group 1) was the commonest etiology (19%), while SSc-ILD-PH (WSPH Group 3) and the left ventricular (LV) dysfunction group (WSPH Group 2) had 6% each.[12]

Screening

Given the high prevalence and the lifetime risk for the development of PH in patients with SSc, screening is an important strategy for the early identification of all phenotypes of SSc-PH, especially SSc-PAH. While there have been various, clinical, autoimmune antibody, and lung function testing-based associations with the development of PH in the SSc population, none of these parameters have individually been useful from a PH screening standpoint.[13] The current guidelines recommend annual screening with echocardiograms for all patients with SSc.[14,15] The 2015 European Society of Cardiology (ESC)/ European Respiratory Society (ERS) criteria using echocardiographic parameters comprise an effective strategy to screen for SSc-PAH patients.[14] SSc is the only collagen vascular disorder for which such an echocardiogram-based strategy is currently recommended. Screening strategies using composite screening instruments such as the DETECT or ASIG tools can identify patients with SSc-PAH with a high sensitivity and negative predictive value (NPV).[12]

While these composite screening tools were designed primarily with a focus on SSc-PAH, they perform fairly well with regard to detection of groups 2 and 3 PH as well. In a study by Hao et al,[16] the 2015 ESC/ERS criteria, DETECT, and ASIG algorithms all were able to detect any form of SSc-PH with a sensitivity >95%. In that study, the ASIG algorithm had a sensitivity of 95.8%, NPV of 92.3%, and had the highest specificity and positive predictive values of all 3 algorithms. However, it is important to note that this population was enriched for SSc-PAH. In our practice, we have found the ASIG algorithm very easy to operationalize, as it only requires PFT data and a serum N-terminal pro B-type natriuretic peptide level to implement, and both of these clinical variables are easily available in most outpatient practices (Figure 1).

Table 1. Sixth World Symposium on Pulmonary Hypertension Classification[a]

1. PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with:
1.4.1 Connective tissue disease[b]
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement[b]
1.7 Persistent PH of the newborn syndrome
2. PH due to left heart disease[b]
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital or acquired cardiovascular conditions leading to postcapillary PH
3. PH due to lung diseases and/or hypoxia[b]
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4. PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5. PH with unclear and/or multifocal mechanisms
5.1 Hematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

[a]Pulmonary hypertension classifications according to the proceedings from the Sixth World Symposium on Pulmonary Hypertension (WSPH). PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction; HIV: human immunodeficiency virus.

[b]WSPH subgroups prevalent in SSc-PH.

With significant advances in awareness, screening, therapies, and risk stratification, the 1- and 3-year survival rates in incident SSc-PAH patients appear to be similar to those in idiopathic pulmonary arterial hypertension (IPAH) patients, but prospective data from the Pulmonary Hypertension As-

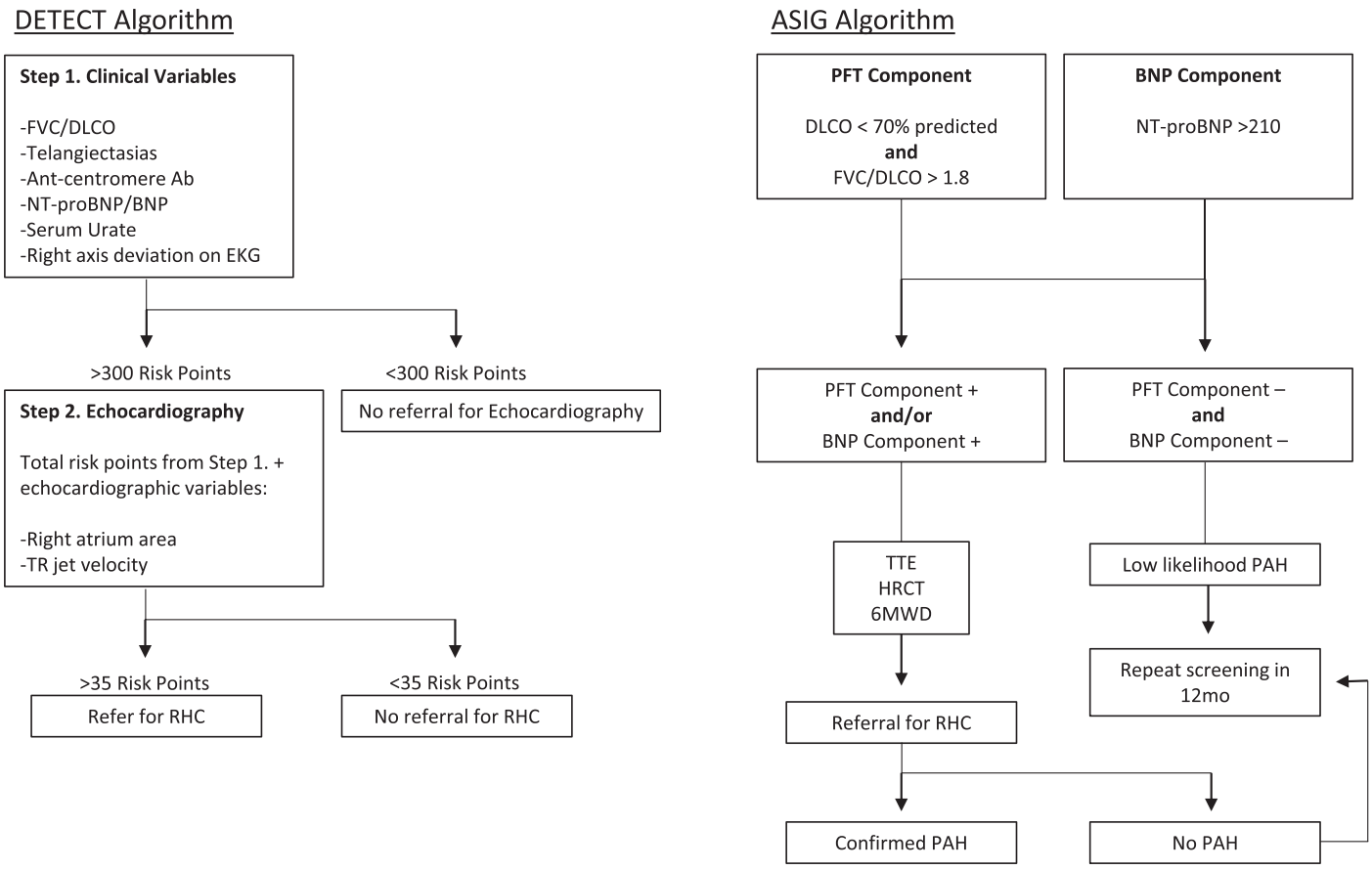

Figure 1: Comparison of systemic sclerosis-associated pulmonary hypertension (SSc-PH) screening algorithms. Side-by-side comparison of screening algorithms for SSc-PH. The DETECT algorithm assigns numerical scores to combined clinical variables using a customized Web-based calculator. This score is used to determine referral for echocardiogram and subsequently right heart catheterization. ASIG algorithm uses PFT and NT-proBNP data to determine patient candidacy for further workup, including RHC. ASIG: Australian Scleroderma Interest Group; NT-proBNP: N-terminal pro B-type natriuretic peptide; DLCO: diffusion capacity of the lung for carbon monoxide; FVC: forced vital capacity; PFT: pulmonary function test; RHC: right heart catheterization; TR: tricuspid regurgitation. Adapted from Hao Y et al.[16]

sessment and Recognition of Outcomes in Scleroderma (PHAROS) registry and other institutional cohorts show that the SSc-PAH population continues to have a long-term survival disadvantage.[17] While lead-time bias could explain some of the improvements in short-term survival rates in the SSc-PAH cohort, earlier intervention with vasodilator therapies and/or diuretics could have prevented or delayed right ventricle (RV) failure and improved survival prospectively.[18] Early detection seems to confer a survival advantage in SSc-PAH when compared with symptom-based evaluation for PAH.[19] Further, 22% of SSc-PAH patients in the PHAROS cohort were asymptomatic at the time of their PAH diagnosis.[20] For this reason, screening for PH and PAH is a valuable strategy in the SSc population.

SSC-PH PHENOTYPES

1. SSc-PAH

While both limited and diffuse SSc patients can develop PAH, the lc SSc phenotype appears to have a higher risk for the development of PAH.[1] PAH is a disease that directly affects the small- to medium-sized pulmonary arteries, leading to vascular remodeling. Initially thought to be analogous to the idiopathic form of PAH, histopathologic analyses more recently suggest that SSc-PAH is a distinct vasculopathy with unique histologic and prognostic characteristics.[21–23] SSc-PAH appears to be different than IPAH, as noted by a lack of plexiform lesions, presence of pulmonary arterial (PA) or arteriolar intimal fibrosis, and some fibrosis of veins or venules.[21] Histologic analyses of SSc-PAH lung tissue have further revealed that PVOD-like lesions and pulmonary vein fibrosis are relatively common in SSc-PAH.[24,25] This may help explain some of the adverse effects associated with the use of PA vasodilators in SSc-PAH patients.

Treatment of SSc-PAH

a. Pulmonary Artery Vasodilators: While there is emerging interest in using adjunctive immunomodulatory agents in the management of SSc-PAH, PA vasodilators are the mainstay of treatment in SSc-PAH. The current guidelines support the use of all PA vasodilators approved for other WSPH group 1 disease patients. These recommendations are based on efficacy and safety data from multiple randomized clinical trials using PA vasodilators that also included SSc-PAH patients.[13,14] There are 3 main pathways currently targeted by available drug therapies: nitric oxide, endothelin,

and prostacyclin pathways. A variety of oral, parenteral, and inhaled formulations are available for the management of SSc-PAH patients.[26]

Most patients now start combination therapy with a phosphodiesterase type V inhibitor (PDE5i) and an endothelin receptor antagonist (ERA). These medications are administered orally and are generally used as first-line agents for PAH owing to their milder side effect profile than prostanoids (prostacyclin pathway analogs). PDE5is were approved for PAH patients after the SUPER and PHIRST trials, both of which included a subset of connective tissue disease-associated PAH (CTD-PAH) (including SSc-PAH) patients.[27,28]

ERAs target endothelin receptors on vascular smooth muscle, thereby preventing the vasoconstrictive effect of circulating endothelin proteins. Ambrisentan, macitentan, and bosentan are the currently approved ERAs. ERA therapy has been shown to improve quality of life and exercise tolerance via 6-minute walk distance (6MWD) in CTD-PAH and SSc-PAH patients, although the beneficial effects in these patients may be attenuated when compared with patients with IPAH.[29–31]

Prostanoids act mainly via binding to the prostacyclin (IP) receptors, activating adenylate cyclase, resulting in the production of cAMP, reducing Ca^{+2} concentrations, and causing vasodilation. To this day, intravenous (IV) prostanoids remain the most potent therapy offered for SSc-PAH patients.[13] Epoprostenol, treprostinil and the IP receptor agonist selexipag are the prostanoids approved for PAH therapy. Epoprostenol is only available in an IV formulation, while treprostinil is available in oral, parenteral, and inhaled routes. Selexipag is administered via the oral route. All the prostanoid formulations have been shown to improve the functional capacity and exercise tolerance (6MWD) in PAH patients, including SSc-PAH patients.[32–36] It is also important to note that optimization of PH in SSc patients involves the use of diuretics, management of arrhythmias, conduction abnormalities, and treatment of coexisting comorbidities such as sleep apnea.[14,37]

b. Immunomodulator Therapy: As noted above, while SSc-PAH is a unique pulmonary vasculopathy, SSc has also been shown to impact the RV adaptation to this pulmonary arteriopathy, which contributes to a greater morbidity and mortality in SSc-PAH.[38] Further, since SSc is a multiorgan disease with an established etiopathogenic basis in immune dysregulation, strategies using immunomodulator therapies as adjuncts in the management of SSc-PAH have garnered some attention. Three categories of immunomodulators studied to date are (a) immunosuppressive, (b) anti-inflammatory, and (c) antiproliferative agents.

A single-institutional, retrospective cohort study exploring the use of immunosuppressive therapy (cyclophosphamide, glucocorticoids) previously showed no benefits in the SSc-PAH population.[39] B-cell depletion, on the other hand, seems to hold some promise. A multicenter, placebo-controlled trial showed that rituximab is safe and well tolerated in SSc-PAH and showed a significant improvement in 6MWD at 48 weeks. Although the study did not meet its a priori established primary outcome, it should be noted that the study was hampered by poor enrollment that forced an alteration of the study design midway through the study.[40]

The antiproliferative agent imatinib, a tyrosine kinase inhibitor was shown in the IMPRES trial to improve 6MWD and hemodynamics among PAH patients including SSc-PAH patients; however, its utility has been called into question due to serious adverse events (intracranial hemorrhage).[41] The CATALYST trial (NCT0265735) evaluating the use of bardoxolone, an NF-κB inhibitor and novel anti-inflammatory agent, in patients with CTD-PAH had to be ended prematurely during the COVID-19 pandemic, after preliminary analyses showed that the study was unlikely to meet its primary endpoint of 6MWD improvement.

Correction of the imbalance in transforming growth factor (TGF) β/BMP signaling appears to hold promise in all forms of PAH including SSc-PAH. While preliminary phase 2 data from FK-506 (tacrolimus) use in PAH showed favorable safety data, therapeutic efficacy was not significant.[42] More recently, the PULSAR trial, another phase 2 study, evaluated the efficacy for sotatercept, a novel TGFβ ligand trap, in PAH.[43] Sotatercept was shown to improve exercise capacity and improve pulmonary vascular hemodynamics in WSPH group 1 PAH patients that included a small number of SSc-PAH patients. Sotatercept is now being studied in multiple phase 3 studies (NCT04576988, NCT04896008, NCT04811092), and SSc-PAH patients are eligible. The new developments in the field of PAH therapeutics are paving a promising and imminent path forward for a more precise and targeted treatment of SSc-PAH.

Prognosis and Risk Stratification

Even though SSc-PAH patients are considered WSPH group 1 and their current management guidelines are similar to those of IPAH patients, the treatment response and prognostic trends of SSc-PAH patients are very different when compared to IPAH patients.[44] While SSc-PAH is a unique pulmonary vasculopathy when compared with IPAH, SSc patients have also been shown to have impaired RV function that is independent of the pulmonary vascular load.[45] In comparison with IPAH, SSc-PAH patients have also been shown to have a reduced RV contractile reserve.[46,47] Further, RV function in SSc-PAH patients does not appear to improve when compared with IPAH patients, despite the up-titration in PA vasodilator therapies over the course of the disease.[48] Therefore, RV maladaptation in SSc-PAH patients is another important contributor to the worsened morbidity and mortality when compared with IPAH patients. While all etiopathogenic mechanisms underlying this RV dysfunction have not been elucidated, 2 major mechanisms appear to be (1) abnormal increase in myocardial fibrosis and (2) diminished myofilament calcium sensing and contractile force.[38]

As previously noted, while there appear to be some short-term survival improvements, SSc-PAH patients continue to have a long-term survival disadvantage.[17] Clinical experience also suggests the presence of multiple SSc-PAH

phenotypes, with some "endo-phenotypes" exhibiting a particularly aggressive disease form and others demonstrating a more stable clinical course. Early and periodic risk assessment could potentially identify those patients at high risk for early decompensation.[49] The 2 widely used risk prediction algorithms are the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL 2.0) risk calculator and the 2015 ESC/ERS risk stratification guidelines.[14,50] The calculator is able to stratify PAH patients into low (<5% 1-year mortality), intermediate (5%–10% 1-year mortality), and high risk (>10% 1-year mortality) categories using a number of clinical variables.[50] The REVEAL 2.0 risk calculator was originally developed for all WSPH group 1 patients and has since been validated in an SSc-PAH cohort; however, it is limited in its ability to predict survival in some of the highest risk SSc-PAH patients.[49]

2. PVOD/PCH

PVOD and PCH are both expressions of the same pulmonary vascular disease which is a subset of WSPH group 1 PAH (1.6). Of all the CTDs, SSc appears to have the strongest association with PVOD/PCH. While the exact incidence and prevalence in SSc patients is unknown, the lc variant of SSc seems to have a predilection for PVOD. PVOD affects the small postcapillary venules, causing a directly postcapillary form of PH that can be difficult to diagnose.[24] The hemodynamic features noted during RHC are like that of an SSc-PAH patient, and so it is challenging to differentiate this disease from PAH. HRCT imaging often reveals signs of PVOD such as interlobular septal thickening, centrilobular ground glass opacities, mediastinal lymphadenopathy, and sometimes pleural effusions. PVOD patients also tend to exhibit more hypoxemia and a significantly lower DLCO.[51] Vasodilator therapy often is not tolerated, and patients can develop pulmonary edema from potent therapies such as ERAs and prostanoids. Disease course is progressive and fatal, and lung transplantation remains the only definitive treatment.

3. SSc-ILD-PH

ILD remains the most common cause of death in SSc patients.[52] Progressive parenchymal fibrosis leads to chronic alveolar hypoxia, hypoxic pulmonary vasoconstriction, and arteriolar remodeling in addition to a progressive loss of pulmonary vascular surface area. These adverse alterations in the pulmonary vasculature lead to elevated pulmonary artery pressures and PH. The dc SSc patients have a higher predilection for the development of ILD.[1] The prevalence of ILD in SSc is estimated to be 25%–50%. While the estimated prevalence of PH in idiopathic pulmonary fibrosis (IPF) is thought to be 30%–50%, the exact prevalence of SSc-ILD-PH is not known.[53] In the DETECT study, which included patients with forced vital capacity (FVC) > 40% predicted and DLCO < 60% predicted, the prevalence of SSc-ILD-PH was 6%.[12] Despite the high prevalence of SSc-ILD, WSPH group 3 PH is not as common as SSc-PAH.[54,55] However, the prognosis of SSc-PH with ILD is particularly poor and likely the worst of any form of SSc-PH, with an estimated 3-year survival rate of 35%.[56]

Parenchymal abnormalities and interstitial changes are widely prevalent in SSc patients. The Sixth WSPH guidelines on group 3 PH define significant parenchymal disease (from a PH standpoint) as FVC < 70% predicted and CT chest that shows extensive parenchymal involvement.[57] Clinical trials of oral or IV PA vasodilators have mostly resulted in no clinical benefits for patients with all forms of ILD-related PH, including SSc-ILD-PH patients. Inhaled prostacyclins seem to hold particular promise in SSc-ILD-PH.[58] The major advantage of inhaled therapy is direct drug delivery to the pulmonary vasculature and, more specifically, direct delivery through functional or ventilating lung tissue without disrupting VQ matching. The recently concluded INCREASE trial in patients with ILD-PH demonstrated that inhaled treprostinil improved exercise capacity when compared with placebo.[58] In that trial, 22% of the participants had underlying CTD, including SSc.

It is important to recognize that, before considering inhaled vasodilator therapies for the ILD-PH patient, the patient's lung disease or hypoxia (supplemental oxygen) and possible coexisting sleep apnea must be addressed first. Similarly, disease-modifying immunosuppression with mycophenolate mofetil or cyclophosphamide may be used to prevent further limit inflammation and progression of pulmonary fibrosis.[59,60] The SENSCIS study demonstrated the efficacy of nintedanib either in isolation or in combination with immunosuppressive therapies in decreasing the rate of progression of SSc-ILD.[61] There is now an emerging role of IL-6 inhibition (tocilizumab) in the management of SSc-ILD.[62,63] Prevention of progression of fibrosis directly slows down the rate of loss of pulmonary vascular surface area and may impact the progression of PH in this disease group. Once ILD management has been optimized, it is reasonable to evaluate and treat residual PH, as discussed below.

Given the high prevalence of some degree of ILD in almost all patients with SSc, differentiating group 1 from group 3 disease can be particularly challenging. Often, patients present with significant pulmonary vascular disease in the background of extensive ILD. These patients would benefit from being cared in pulmonary vascular disease programs with experience in managing SSc-PH patients. In Figure 2 and Table 2, we highlight our approach to the management of an SSc patient with suspected PH.

4. SSc-Associated LV Myocardial Dysfunction-Related PH (SSc-LVD-PH)

SSc can lead to myocardial fibrosis and LV dysfunction resulting in pulmonary venous congestion and subsequent WSPH group 2 PH.[10,37] These patients exhibit an elevated PCWP on RHC, in addition to an elevated mPAP. In addition to primary myocardial inflammation and fibrosis, microvascular coronary disease in SSc may also contribute to myocardial damage.[64] The prevalence of cardiac involvement is estimated to be 50%–80% on autopsy studies; however, clinical heart

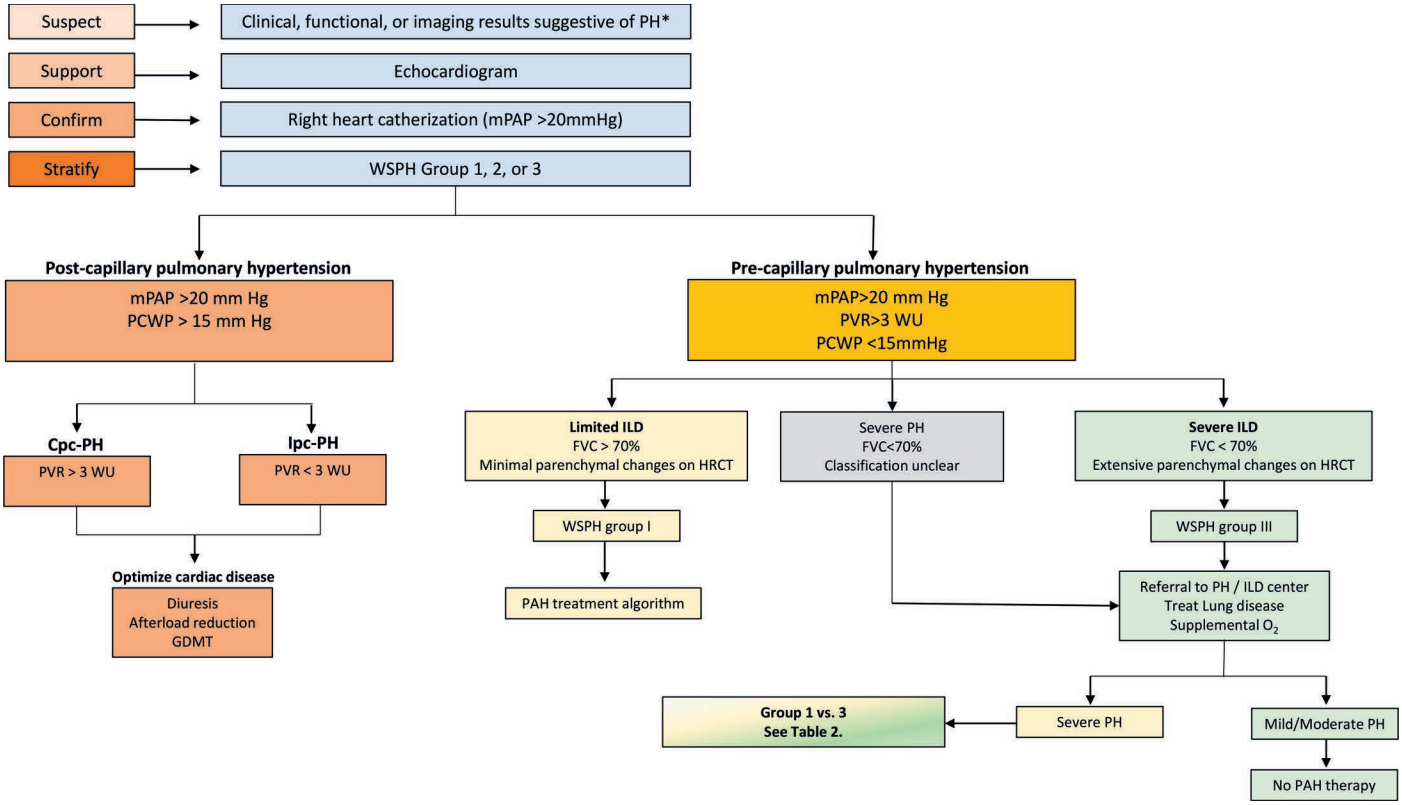

Figure 2: Systemic sclerosis-associated pulmonary hypertension (SSc-PH) algorithm. Proposed approach to screening, diagnosis, subgroup classification, and management of SSc-PH patients. *Clinical findings suggestive of PH may include progressive dyspnea, exercise intolerance, signs of right heart failure on exam, loud P2, electrocardiogram with right ventricle strain, elevated B-type natriuretic peptide, or reduced 6 minute walk distance. CI: cardiac index; Cp-PH: combined precapillary and postcapillary PH; DLCO: diffusion capacity of the lung for carbon monoxide; ERA: endothelin receptor antagonist; FVC: forced vital capacity; GDMT: guideline-directed medical therapy; HRCT: high-resolution computed tomography; Ipc-PH: isolated postcapillary PH; ILD: interstitial lung disease; mPAP: mean pulmonary artery pressure; PCA: prostacyclin agonist; PCWP: pulmonary capillary wedge pressure; PDE5i: phosphodiesterase type V inhibitor; PVR: pulmonary vascular resistance; WSPH: World Symposium on Pulmonary Hypertension; WU: Woods units. Adapted with permission of the © ERS 2021.[57]

failure symptoms are less common.[65] Diastolic dysfunction leading to heart failure with preserved ejection fraction (HFpEF) is the predominant presentation of cardiac involvement in SSc on echocardiography, estimated to affect 20%–45% of patients.[7,66] Occult LV dysfunction is also often unmasked during the management of precapillary PH in SSc patients, often when assessing response to PA vasodilator therapies.[66]

There are currently no SSc-LVD-PH-specific guidelines outside of volume management, diuretic therapy, and periodic monitoring for the development of superadded pulmonary vascular disease later in the disease course. The ongoing research in the field of HFpEF therapeutics could soon yield adjunctive therapies for the management of SSc-LVD-PH patients.

OVERVIEW OF THE MANAGEMENT OF THE SSC PATIENT WITH SUSPECTED PH

Treatment of PH in an SSc patient can be quite challenging given the coexistence of different and competing phenotypes of pulmonary vascular disease, heterogeneity of disease progression, and treatment response. In our experience, there are 3 essential principles for managing PH in the SSc population:

(1) Identifying the appropriate phenotype is important, and often utilizing an expert PH and ILD center with experience in the management of these patients is helpful (Figure 2). In our experience, one of the most challenging aspects of caring for SSc patients with PH is accurate phenotyping. As was highlighted earlier, identifying significant pulmonary vascular disease that is "layered" on top of the background ILD can be an incredibly challenging endeavor.[67,68] While there has been important work done in this area, we use an approach similar to that highlighted by Forfia et al[67] to differentiate the SSc-ILD/chronic obstructive pulmonary disease patient with significant pulmonary vascular disease from the SSc-ILD-PH patient (Table 2).

(2) Risk stratification at baseline and follow-up visits is important to monitor response to therapy and also for consideration of early referral for lung transplantation in nonresponders. It is important to note that the current risk stratification algorithms are validated for use in SSc-PAH patients and are not validated for use in other phenotypes of PH in the SSc population.

(3) Lack of improvement in the quality of life with therapy should prompt reconsideration of the phenotype of PH. Use of PA vasodilators currently is

Table 2. Differentiating World Symposium on Pulmonary Hypertension (WSPH) phenotypes in systemic sclerosis (SSc) patients with lung disease and pulmonary hypertension (PH)[a]

Clinical parameter	Favors WSPH Group 1	Favors WSPH Group 3
Clinical features	Signs of RV failure: Elevated JVP, +AJR	May or may not have signs of RV failure
EKG	RV strain Right-axis deviation RV hypertrophy	May or may not have evidence of RV strain
PFT	FVC < 70% predicted FVC/DLCO > 1.8	FVC < 70% predicted FVC/DLCO < 1.8
Chest imaging	No significant ILD Extent of disease <30%	Severe ILD Extent of disease >30%
Echocardiography	RV/LV ratio > 1.0 TAPSE < 20 mm Moderate-severe systolic IVS flattening Late or midsystolic notching of doppler FVE in RVOT	RV/LV ratio 0.6–1.0 TAPSE > 20 mm Mild systolic IVS flattening Late systolic or no notching of doppler FVE in RVOT
RHC	RAP > 15 mm Hg CI < 2.5 $^{l\text{-}min\text{-}1}$-m^2 PVR > 6 WU	RAP < 15 mm Hg CI ≥ 2.5 $^{l\text{-}min\text{-}1}$-m^2 PVR < 6 WU
CPET	Breathing reserve < 20% O_2 pulse reduced VE/VCO_2 slope significantly increased	Breathing reserve < 20% O_2 pulse normal VE/VCO_2 slope normal or slightly increased

[a]Evaluation of the complex SSc patient with PH and lung disease. Evaluation of different clinical parameters may help identify patients favoring a WSPH group 1 or a WSPH group 3 phenotype and which patients may have a positive response to pulmonary vasodilator therapy. AJR: abdomino-jugular reflux; CI: cardiac index; CPET: cardiopulmonary exercise testing; DLCO: diffusion capacity of the lung for carbon monoxide; EKG: electrocardiogram; FVC: forced vital capacity; FVE: flow velocity envelope; ILD: interstitial lung disease; IVS: interventricular septum; JVP: jugular venous pressure; LV: left ventricle; PFT: pulmonary function test; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RHC: right heart catheterization; RV: right ventricle; RVOT: right ventricular outflow tract; TAPSE: tricuspid annular plane systolic excursion; VCO_2: volume of exhaled carbon dioxide; VE: expired ventilation; WU: Woods units. Table adapted from Forfia et al. [67]

reserved for treatment in the SSc-PAH population, while inhaled vasodilators seem to hold promise for the management of SSc-ILD-PH. Use of PA vasodilators in the other phenotypes of PH in the SSc population is not encouraged outside of clinical trials at this time.

SUMMARY

SSc-PH comprises multiple phenotypes, and an accurate identification of the phenotype of pulmonary vascular disease is critical to the successful management of these patients. Screening is important to identify patients at an early stage to be able to effectively delay or prevent the progression to RV failure. SSc-associated pulmonary vascular disease is unique, and novel therapeutic targets could lead to a more tailored approach to treating this challenging group of patients.

References

1. Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103):1685–1699.
2. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72(11):1747–1755.
3. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis*. 2007;66(7):940–944.
4. Sahay S. Evaluation and classification of pulmonary arterial hypertension. *J Thorac Dis*. 2019;11(Suppl 14):S1789–S1799.
5. Chaisson NF, Hassoun PM. Systemic sclerosis-associated pulmonary arterial hypertension. *Chest*. 2013;144(4):1346–1356.
6. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982–2006. *Eur Respir J*. 2007;30(6):1103–1110.
7. Avouac J, Airò P, Meune C, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *J Rheumatol*. 2010;37(11):2290–2298.
8. Chang B, Wigley FM, White B, Wise RA. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. *J Rheumatol*. 2003;30(11):2398–2405.
9. Vemulapalli S, Cohen L, Hsu V. Prevalence and risk factors for left ventricular diastolic dysfunction in a scleroderma cohort. *Scand J Rheumatol*. 2017;46(4):281–287.
10. van Wijngaarden SE, Ben Said-Bouyeri S, Ninaber MK, et al. Progression of left ventricular myocardial dysfunction in systemic sclerosis: a speckle-tracking strain echocardiography study. *J Rheumatol*. 2019;46(4):405–415.
11. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913. doi:10.1183/13993003.01913-2018
12. Coghlan JG, Denton CP, Grünig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis*. 2014;73(7):1340–1349.
13. Argula RG, Ward C, Feghali-Bostwick C. Therapeutic challenges and advances in the management of systemic sclerosis-related pulmonary arterial hypertension (SSc-PAH). *Ther Clin Risk Manag*. 2019;15:1427–1442.
14. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67–119.
15. Khanna D, Gladue H, Channick R, et al. Recommendations for screening and detection of connective tissue disease-associated pulmonary arterial hypertension. *Arthritis Rheum*. 2013;65(12):3194–3201.
16. Hao Y, Thakkar V, Stevens W, et al. A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. *Arthritis Res Ther*. 2015;17(1):7. doi:10.1186/s13075-015-0517-5.
17. Kolstad KD, Li S, Steen V, Chung L, PHAROS Investigators. Long-term outcomes in systemic sclerosis-associated pulmonary arterial hypertension from the Pulmonary Hypertension Assessment and Recognition of

Outcomes in Scleroderma registry (PHAROS). *Chest*. 2018;154(4):862–871.
18. Weatherald J, Montani D, Jevnikar M, Jaïs X, Savale L, Humbert M. Screening for pulmonary arterial hypertension in systemic sclerosis. *Eur Respir Rev*. 2019;28(153):190023. doi:10.1183/16000617.0023-2019
19. Humbert M, Yaici A, de Groote P, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. *Arthritis Rheum*. 2011;63(11):3522–3530.
20. Chung L, Domsic RT, Lingala B, et al. Survival and predictors of mortality in systemic sclerosis-associated pulmonary arterial hypertension: outcomes from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry. *Arthritis Care Res (Hoboken)*. 2014;66(3):489–495.
21. Overbeek MJ, Vonk MC, Boonstra A, et al. Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. *Eur Respir J*. 2009;34(2):371–379.
22. Rabinovitch M, Guignabert C, Humbert M, Nicolls MR. Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension. *Circ Res*. 2014;115(1):165–175.
23. Tuder RM, Stacher E, Robinson J, Kumar R, Graham BB. Pathology of pulmonary hypertension. *Clin Chest Med*. 2013;34(4):639–650.
24. Günther S, Jaïs X, Maitre S, et al. Computed tomography findings of pulmonary venoocclusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. *Arthritis Rheum*. 2012;64(9):2995–3005.
25. Dorfmüller P, Humbert M, Perros F, et al. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. *Hum Pathol*. 2007;38(6):893–902.
26. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med*. 2004;351(14):1425–1436.
27. Badesch DB, Hill NS, Burgess G, et al. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. *J Rheumatol*. 2007;34(12):2417–2422.
28. Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119(22):2894–2903.
29. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346(12):896–903.
30. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008;117(23):3010–3019.
31. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809–818.
32. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med*. 1996;334(5):296–301.
33. Menon N, McAlpine L, Peacock AJ, Madhok R. The acute effects of prostacyclin on pulmonary hemodynamics in patients with pulmonary hypertension secondary to systemic sclerosis. *Arthritis Rheum*. 1998;41(3):466–469.
34. White RJ, Jerjes-Sanchez C, Bohns Meyer GM, et al. Combination therapy with oral treprostinil for pulmonary arterial hypertension. A double-blind placebo-controlled clinical trial. *Am J Respir Crit Care Med*. 2020;201(6):707–717.
35. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915–1922.
36. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522–2533.
37. Hung G, Mercurio V, Hsu S, Mathai SC, Shah AA, Mukherjee M. Progress in understanding, diagnosing, and managing cardiac complications of systemic sclerosis. *Curr Rheumatol Rep*. 2019;21(12):68. doi:10.1007/s11926-019-0867-0
38. Hsu S, Kokkonen-Simon KM, Kirk JA, et al. Right ventricular myofilament functional differences in humans with systemic sclerosis-associated versus idiopathic pulmonary arterial hypertension. *Circulation*. 2018;137(22):2360–2370.
39. Sanchez O, Sitbon O, Jaïs X, Simonneau G, Humbert M. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest*. 2006;130(1):182–189.
40. Zamanian RT, Badesch D, Chung L, et al. Safety and efficacy of B-cell depletion with rituximab for the treatment of systemic sclerosis associated pulmonary arterial hypertension: a multi-center, double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2021. doi:10.1164/rccm.202009-3481OC
41. Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation*. 2013;127(10):1128–1138.
42. Spiekerkoetter E, Sung YK, Sudheendra D, et al. Randomised placebo-controlled safety and tolerability trial of FK506 (tacrolimus) for pulmonary arterial hypertension. *Eur Respir J*. 2017;50(3):1602449. doi:10.1183/13993003.02449-2016
43. Humbert M, McLaughlin V, Gibbs JSR, et al. Sotatercept for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2021;384(13):1204–1215.
44. Rhee RL, Gabler NB, Sangani S, Praestgaard A, Merkel PA, Kawut SM. Comparison of treatment response in idiopathic and connective tissue disease-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2015;192(9):1111–1117.
45. Tedford RJ, Mudd JO, Girgis RE, et al. Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. *Circ Heart Fail*. 2013;6(5):953–963.
46. Hsu S, Houston BA, Tampakakis E, et al. Right ventricular functional reserve in pulmonary arterial hypertension. *Circulation*. 2016;133(24):2413–2422.
47. Kelemen BW, Mathai SC, Tedford RJ, et al. Right ventricular remodeling in idiopathic and scleroderma-associated pulmonary arterial hypertension: two distinct phenotypes. *Pulm Circ*. 2015;5(2):327–334.
48. Argula RG, Karwa A, Lauer A, et al. Differences in right ventricular functional changes during treatment between systemic sclerosis-associated pulmonary arterial hypertension and idiopathic pulmonary arterial hypertension. *Ann Am Thorac Soc*. 2017;14(5):682–689.
49. Mullin CJ, Khair RM, Damico RL, et al. Validation of the REVEAL prognostic equation and risk score calculator in incident systemic sclerosis-associated pulmonary arterial hypertension. *Arthritis Rheumatol*. 2019;71(10):1691–1700.
50. Benza RL, Gomberg-Maitland M, Elliott CG, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL Risk Score Calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest*. 2019;156(2):323–337.
51. Montani D, Lau EM, Dorfmüller P, et al. Pulmonary veno-occlusive disease. *Eur Respir J*. 2016;47(5):1518–1534.
52. Schoenfeld SR, Castelino FV. Evaluation and management approaches for scleroderma lung disease. *Ther Adv Respir Dis*. 2017;11(8):327–340.
53. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J*. 2015;46(4):1113–1130.
54. Launay D, Remy-Jardin M, Michon-Pasturel U, et al. High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. *J Rheumatol*. 2006;33(9):1789–1801.
55. Nihtyanova SI, Schreiber BE, Ong VH, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol*. 2014;66(6):1625–1635.
56. Lefèvre G, Dauchet L, Hachulla E, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. *Arthritis Rheum*. 2013;65(9):2412–2423.
57. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J*. 2019;53(1):1801914. doi:10.1183/13993003.01914-2018

58. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med*. 2021;384(4):325–334.
59. Liossis SN, Bounas A, Andonopoulos AP. Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. *Rheumatology (Oxford)*. 2006;45(8):1005–1008.
60. Nannini C, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. *Arthritis Res Ther*. 2008;10(5):R124. doi:10.1186/ar2534
61. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med*. 2019;380(26):2518–2528.
62. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet*. 2016;387(10038):2630–2640.
63. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963–974.
64. Allanore Y, Meune C. Primary myocardial involvement in systemic sclerosis: evidence for a microvascular origin. *Clin Exp Rheumatol*. 2010;28(5 Suppl 62):S48–S53.
65. Follansbee WP, Miller TR, Curtiss EI, et al. A controlled clinicopathologic study of myocardial fibrosis in systemic sclerosis (scleroderma). *J Rheumatol*. 1990;17(5):656–662.
66. Fox BD, Shimony A, Langleben D, et al. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. *Eur Respir J*. 2013;42(4):1083–1091.
67. Forfia PR, Vaidya A, Wiegers SE. Pulmonary heart disease: the heart-lung interaction and its impact on patient phenotypes. *Pulm Circ*. 2013;3(1):5–19.
68. King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease: dilemmas in diagnosis and the conundrum of treatment. *Chest*. 2020;158(4):1651–1664.