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SCLERODERMA (J VARGA, SECTION EDITOR)

An Update on Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: a Review of the Current Literature

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Abstract

Purpose of Review This review will summarize the most current literature on the clinical impact, epidemiology, risk factors, screening recommendations, predictors of outcomes, and treatment options in patients with pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc).

Recent Findings PAH continues to be a major cause of morbidity and mortality in SSc. Many risk factors and predictors of outcomes have been identified in patients with SSc including clinical, hemodynamic, and laboratory parameters. Screening for PAH in SSc patients is important and screening algorithms have been developed. Despite many available treatment options for PAH, prognosis remains poor.

Summary Awareness of risk factors, early detection, and up-front combination treatment are important considerations in SSc-PAH and may lead to improved outcomes. Further research to develop better biomarkers and therapies is needed to continue to improve survival and outcomes in patients with SSc-PAH.

Keywords Systemic sclerosis · Pulmonary hypertension · SSc · PAH · Scleroderma · Connective tissue disease

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease (CTD) characterized by multi-organ vasculopathy and fibrosis. Pulmonary hypertension (PH) is a known complication of SSc and other connective tissue diseases. Pulmonary hypertension is classified into five groups by the World Health Organization (WHO). WHO group 1, pulmonary arterial hypertension (PAH) is defined as a mean pulmonary arterial pressure (mPAP) greater than 25 mmHg and pulmonary arterial wedge pressure (PAWP) less than 15 mmHg on right heart catheterization (RHC) in the absence of significant interstitial lung disease (ILD) (only mild ILD on chest imaging and forced vital capacity (FVC) and total lung capacity (TLC) greater than 70% predicted) [1].

In this review, we will summarize the most current literature regarding the clinical impact, epidemiology, risk factors, screening recommendations, predictors of outcomes, and treatments in patients with SSc-PAH.

Clinical Impact

PAH is a major cause of morbidity and mortality in SSc [2, 3]. In a US study evaluating the major causes of death in SSc from the 1970s through 2001, pulmonary fibrosis and PAH replaced scleroderma renal crisis as the most common causes of death over time [2]. A more recent study in Spain confirmed these findings in a cohort of 879 patients, 138 of whom died, with the most common causes of death being PH, PH-ILD, and ILD [4]. In this cohort, PH was the cause of death in 17% of patients. Another large multinational study of SSc patients from Australia, Canada, and Spain showed that SSc-PAH patients had a significantly increased risk of death compared to those without PAH (HR 2.50, 95% CI 1.83–3.42, $p < 0.0001$) [3].

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Patients with SSc and PAH have been shown to have a higher mortality than patients with PAH from other causes [5, 6]. A UK study of 322 patients with idiopathic pulmonary arterial hypertension (IPAH) and 329 patients with SSc-PAH found an estimated median survival of 7.8 years in IPAH compared to 3 years in SSc-PAH ($p < 0.001$) [5]. Additionally, individuals with SSc-PAH have a higher mortality than non-SSc connective tissue disease-associated PAH (non-SSc-CTD-PAH) [7, 8]. A multicenter US registry (the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL)) found that the 3-year survival in previously and newly diagnosed patients with SSc-PAH was 61 and 51%, respectively, compared with 81 and 76% in non-SSc-CTD-PAH patients ($p < 0.001$) [7]. In particular, studies have shown better outcomes in patients with systemic lupus erythematosus (SLE)-PAH compared with those with SSc-PAH. A national registry study from the UK demonstrated a better 3-year survival rate in SLE-PAH compared to SSc-PAH (74 vs 47%, p=0.01) [8]. Another cohort study from China found a better 3-year survival rate of 64% in SSc-PAH patients, but this was still worse than those with SLE-PAH (81%, $p < 0.05$) [9].

Epidemiology

The prevalence of PAH in SSc has been estimated to be between 5 and 12% [10, 11, 12•, 13]. A French study of 384 SSc patients followed for 3 years showed an incidence of 1.37 per 100 patient-years for PH, and 0.61 per 100 patient-years for PAH [14]. In the US Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort, 251 SSc patients who were at high risk of developing PH based on pulmonary function test (PFT) and echocardiographic parameters (diffusing capacity of carbon monoxide (DLCO) < 55% predicted, forced vital capacity (FVC)/DLCO ratio > 1.6, and/or right ventricular systolic pressure (RVSP) > 40 mmHg) were followed for a mean of 2.5 years. RHC was performed if clinically indicated and PH developed in 10% at 2 years, 13% at 3 years, and 25% at 5 years, while PAH developed in 7% at 2 years, 9% at 3 years, and 17% at 5 years [15]. In a Belgian study of 195 consecutively-enrolled SSc patients followed for 1 year, the annual incidence of PAH was 1.5% [16]. The Australian Scleroderma Cohort Study (ASCS) of 1636 SSc patients found a similar annual incidence of 1.4% over a study period of 9 years [17].

Gender differences have also been observed in SSc-PAH. In a Canadian study of 378 SSc-PAH patients, males had a shorter mean time to PAH diagnosis (1.7 ± 14 vs. 5.5 ± 14.2 years, standardized difference 93%) and shorter PAH duration (3.5 ± 3.1 vs. 4.7 ± 4.2 years, standardized difference 29%) but only a trend toward worse survival in males compared with females (5-year survival 46 vs. 57%, $p = 0.07$) [18].

Risk Factors

Various risk factors for development of PAH in SSc have been described (Table 1). Older age [5, 13, 19], late onset of disease (age ≥ 60 years) [19], and post-menopausal status [20] have been associated with an increased risk of PAH in SSc patients. While patients who have had SSc for longer are at increased risk of developing PAH [13, 21], this complication can also affect patients who have had SSc for less than 5 years [22]. The limited cutaneous subtype of SSc has been associated with an increased risk of SSc [21] though patients with diffuse cutaneous disease can also develop PAH [22].

Clinically evident vascular phenomena have also been associated with risk of PAH in SSc [23]. Increased numbers of matted telangiectasias have been found to be correlated with elevated RVSP and higher odds of developing PAH by RHC during follow-up [23]. In addition, pseudotumoral telangiectasias (> 5 mm in diameter) increased the odds of precapillary pulmonary hypertension by more than 12-fold in multivariate analysis (OR 12.60 [95% CI 1.68–94.53]) [24]. History of digital ulcers has also been found to be associated with risk of PAH in SSc [12•, 21, 25].

Non-invasive pulmonary and cardiac testing can also help with risk assessment for PAH in patients with SSc. Certain PFT parameters are predictive of PAH. Isolated low DLCO (< 50% predicted) [5, 26], DLCO/alveolar volume (AV) less than 70% [13] and reduced DLCO relative to FVC (FVC%/DLCO% ratio greater than 1.6) [27–29] have all been associated with increased risk of PAH in SSc. On echocardiography, the yearly rate of increase in RVSP is associated with increased risk of PAH and mortality [30]. In this study of 613

Table 1 Risk factors for PAH in SSc

Demographics
Older age
Late onset of disease
Post-menopausal status
Vascular phenomena
Increased/pseudotumoral telangiectasias
Digital ulcers
Pulmonary function test (PFT) parameters:
Isolated low DLCO (< 50% predicted)
DLCO/alveolar volume (AV) < 70%
FVC%/DLCO% ratio > 1.6
Transthoracic echocardiogram (TTE) findings
Increase in RVSP > 2 mmHg/year
Right heart catheterization (RHC) findings
mPAP 21–24 mmHg
Transpulmonary gradient (TPG) ≥ 11 mmHg

SSc patients who had at least three transthoracic echocardiograms (TTEs), in patients whose RVSP rose at a rate of 1–1.99, 2–2.22, and 3 + mmHg/year compared to patients with a stable RVSP, the relative hazard for development of PAH was 1.90 (95% CI 0.91,3.96), 5.09 (95% CI 2.53,10.26) and 6.15 (95% CI 3.58,10.56), respectively.

Several studies have evaluated patients with mPAP of 21–24 mmHg, also known as borderline PAH (BoPAH) in SSc, and their risk of developing full-blown PAH. A post hoc analysis of the DETECT study evaluated patients with SSc who did not have a prior diagnosis of PAH and were referred for RHC, and compared BoPAH patients (n=36) to those with normal mPAP (n=148) as well as PAH patients (n=60) to those with BoPAH. This study found that the mean tricuspid regurgitant velocity, transpulmonary gradient (TPG), and pulmonary vascular resistance (PVR) in patients with BoPAH were intermediate between that of patients with normal mPAP and PAH, suggesting that BoPAH may be an intermediate stage on the continuum between normal PA pressures and PAH [31]. The PHAROS cohort compared 35 patients with an initial normal RHC and 28 patients who had BoPAH [32]. Exercise RHC was performed in 16 patients with BoPAH and 18 with normal hemodynamics. Of these, 88% in the BoPAH group had exercise-induced PAH with mPAP ≥ 30 mmHg compared to 56% of those with normal hemodynamics. Additionally, after 2 years of follow-up, 55% of the BoPAH group and 32% of the initially normal hemodynamics group developed PH at rest on repeat RHC. A prospective cohort study from the UK also compared 142 patients with normal mPAP with 86 patients who had BoPAH at baseline [33]. Patients with BoPAH were more likely to develop PH in the follow-up period compared to those with baseline normal hemodynamics ($p < 0.001$, HR 3.7). Furthermore, elevated TPG ≥ 11 mg Hg at baseline was also predictive of development of PH ($p < 0.001$, HR 7.9).

Autoantibodies are important in risk stratification for PAH in SSc patients (Table 2). Anticentromere antibodies (ACA) [13, 34–36], nucleolar pattern of antinuclear antibodies (NUC) [34, 35, 37], anti-U1-ribonucleoprotein (RNP) [35, 38], antiphospholid antibodies against cardiolipin (aCL) and beta2-glycoprotein 1 (beta2-GPI) [39], and the lack of anti-Scl-70 antibody [26, 40] are associated with an increased risk of PAH in patients with SSc. Additional antibodies have also been more recently described in SSc-PAH patients. Anti-endothelial cell antibodies (AECAs) [41] are seen in 22–40% of SSc patients [42–44] and are associated with an increased incidence of digital infarcts/gangrene ($p < 0.01$) and PAH ($p < 0.001$) [45]. Vascular receptor antibodies including anti-endothelin receptor type A antibodies (ETAR) and anti-angiotensin receptor type 1 antibodies (AT1R), which activate endothelial cells and mediate wound repair, are more prevalent and found at higher levels in patients with SSc-PAH than in other forms of pulmonary hypertension including IPAH, chronic thromboembolic pulmonary hypertension, and pulmonary hypertension due to congenital heart disease [46]. Furthermore, follow-up of 253 consecutive patients with SSc in whom 36 were diagnosed with PAH over a mean observation period of 6 years, the presence of anti-AT1R and anti-ETAR was associated with an increased risk of PAH (HR 4.3, 95% CI 2.2–8.4 and HR 3.5, 95% CI 1.51–5.60, respectively) [46].

Table 2 Clinically available and novel autoantibodies associated with SSc-PAH

Clinically available
Anticentromere antibodies (ACA)
Nucleolar pattern of antinuclear antibodies (NUC)
Anti-U1-ribonucleoprotein (RNP)
Antiphospholipid antibodies: cardiolipin (aCL) and beta2-glycoprotein 1 (beta2-GPI)
Absence of Anti-Scl-70/topoisomerase I antibodies
Novel
Anti-endothelial cell antibodies (AECAs)
Anti-endothelin receptor type A antibodies (ETAR)
Anti-angiotensin receptor type 1 antibodies (AT1R)

Screening and Diagnosis

Right heart catheterization (RHC) is the gold standard for diagnosis of PAH [47]. Multiple screening algorithms have been proposed to identify SSc patients at risk of developing PAH with the goal of referring them for RHC (Fig. 1). The European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines are based on symptoms, signs, history, and echocardiographic probability of PH [48]. The Australian Scleroderma Interest Group (ASIG) algorithm is based on N-terminal pro b-type natriuretic peptide (NT-proBNP) levels and pulmonary function tests (PFTs) [49]. The DETECT algorithm includes a step-wise process in which first non-echocardiographic variables (PFT results, telangiectasias, presence of ACA, NT-proBNP, serum urate, and presence of right axis deviation on EKG) are assessed, with subsequent assessment of echocardiographic parameters (right atrium area, tricuspid regurgitant velocity) if a threshold of abnormalities are observed in the first step [50]. RHC is then performed in patients deemed high risk by echocardiographic measures. A recent study confirmed the high sensitivity and negative predictive value of the DETECT algorithm [51]. A modified DETECT calculator, which replaces right atrial area with $(1.4 \times \text{right ventricle diameter})^2$, may be useful if right atrial area is not available [52].

A recent Belgian study compared the DETECT algorithm with the 2009 ESC/ERS guidelines and post hoc with the 2015 ESC/ERS guidelines in 195 SSc patients. Of the three

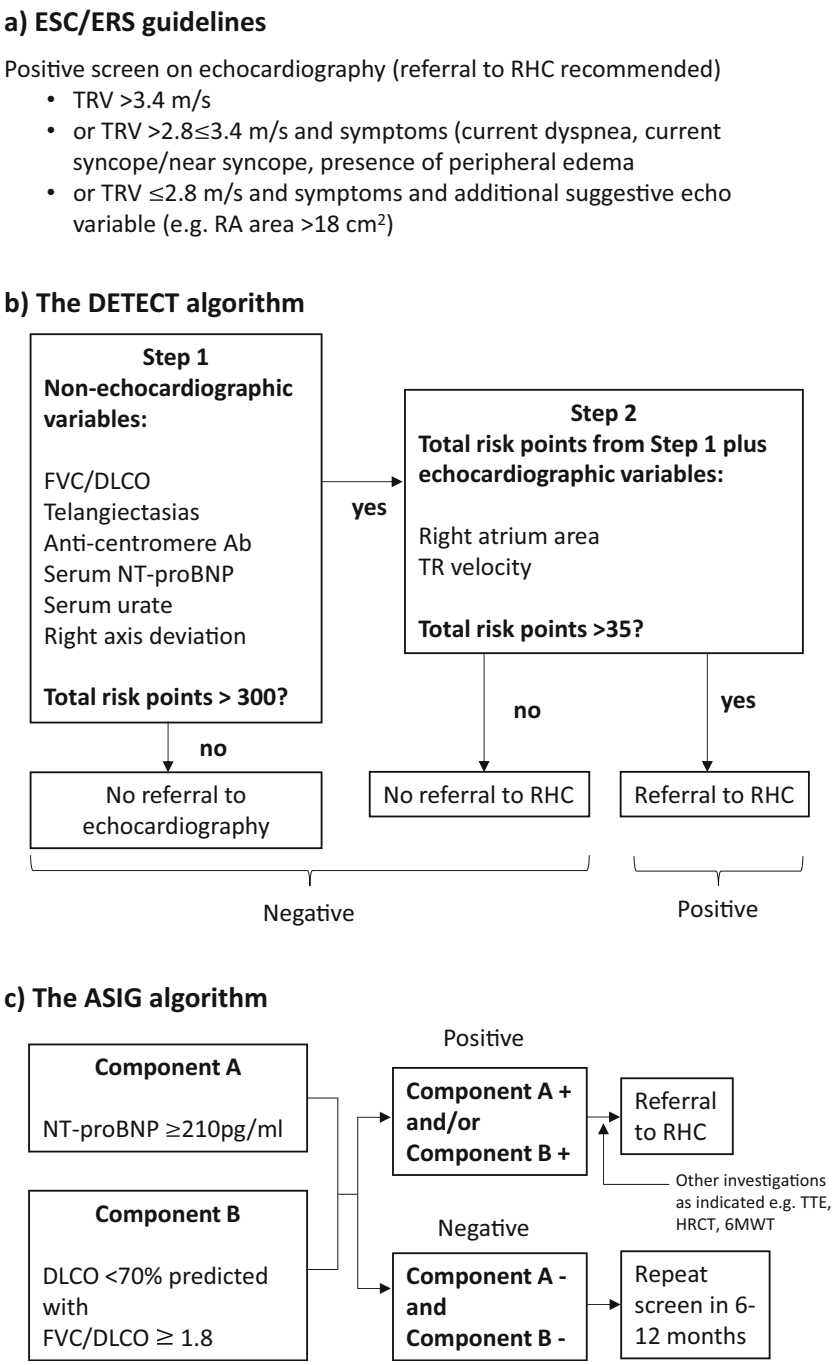

Fig. 1 Summary of screening algorithms. Ab, antibody; ASIG, Australian Scleroderma Interest Group; DLCO, diffusing capacity for carbon monoxide; ESC/ERS, European Society of Cardiology/ European Respiratory Society; FVC, forced vital capacity (percentage predicted); HRCT, high-resolution computed tomography of the chest; RA, right atrium; RHC, right heart catheterization; TR, tricuspid regurgitation; TRV, tricuspid regurgitant velocity; TTE, transthoracic echocardiography. Figure reproduced with permission from BioMed Central, Hao et al. Arthritis Research & Therapy (2015) 17:7 [53•]

patients who were diagnosed with PAH, all three algorithms had recommended RHC. The DETECT algorithm referred the most patients for RHC, but the positive predictive value was only 6% compared with 18% using the 2009 ESC/ERS guidelines alone and 23% when combining the two. The cost per patient was also highest when using DETECT alone [16].

The current screening recommendations state that all patients with SSc should be screened for PAH with PFTs, TTE, and NT-proBNP at baseline and at the time of development of any new signs or symptoms. In addition, PFTs and TTE should be repeated annually [54]. However, adherence to these screening recommendations remains low. An Australian study found that less than half of rheumatologists were screening their patients with SSc of more than 10 years disease duration with annual TTE and PFTs [17].

Multiple studies have evaluated the potential utility of exercise echocardiography for the early detection of PAH in SSc. A recent study evaluated 76 SSc patients with TTE at rest, TTE with exercise on a semi-supine cycle ergometer, RHC at rest and with a supine ergometer [55]. For the noninvasive detection of PH,

systolic pulmonary artery pressure (SPAP) > 40 mmHg on TTE at rest had a 73% sensitivity for PH as confirmed by RHC, compared with 95% sensitivity when using SPAP > 45 mmHg on exercise TTE. Baptista et al. performed a systematic review including 15 studies enrolling 1242 SSc patients to identify exercise-induced increases in SPAP [56]. Several different exercise protocols and positions were used and the definition of a positive test varied widely. The mean estimated SPAP at rest ranged from 18 to 35 mmHg, while at peak exercise it ranged from 30 to 51 mmHg, with half of the studies reporting a mean exercise SPAP of at least 40 mmHg. The mean increase in SPAP was 15 mmHg, with 12–27% of patients deemed to have a positive exercise TTE based on the definition in each respective study. However, many of these studies did not include RHC confirmation for the presence or later development of PAH to correlate with a positive exercise echocardiogram.

Cardiopulmonary exercise testing (CPET) may be a useful non-invasive test for early detection of SSc-PAH. A multicenter German and Austrian study evaluated 173 consecutive patients with SSc, without a diagnosis of PAH, but with potential signs of PAH defined as symptoms, elevated pulmonary artery pressure on echocardiography, reduced DLCO or elevated NT-proBNP [57]. All of these patients underwent CPET followed by RHC. Multiple CPET parameters showed high correlation with pulmonary hemodynamics found on RHC. In particular, peak VO_2 had a reciprocal relationship with mPAP ($r = -0.62$, $p < 0.01$), TPG ($r = -0.60$, $p < 0.01$) and PVR ($r = -0.58$, $p < 0.01$); peak $P_{ET}CO2$ was inversely correlated with mPAP ($r = -0.57$, $p < 0.01$) and TPG ($r = -0.54$, $p < 0.01$); and nadir VE/VCO_2 was positively correlated with mPAP ($r = 0.61$, $p < 0.01$), TPG ($r = 0.59$, $p < 0.01$), and PVR ($r = 0.58$, $p < 0.01$).

Cardiac MRI may also be helpful in the assessment of PAH in SSc patients; however, its role has not been well defined thus far [58]. One study evaluated 40 SSc patients suspected of having PAH who underwent MRI and RHC [59]. Twenty-eight patients were found to have PH on RHC. The ventricular mass index (VMI) was assessed on MRI and found to have strong positive correlations with mPAP ($r = 0.79$) and PVR ($r = 0.8$), and a moderate negative correlation with cardiac index (CI) ($r = -0.65$, $p < 0.0001$ for all). Moreover, cardiac MRI can provide better tissue characterization and assessment of the right and left ventricular function, perfusion defects, and myocardial fibrosis, compared to other imaging modalities. However, given the expense and the fact that a high level of expertise is required for the proper acquisition and interpretation of cardiac MRI images in patients with SSc, this imaging modality may not be appropriate for screening.

Survival and Predictors of Mortality

Clinical, hemodynamic, and serologic features have been described as predictors of mortality in SSc-PAH. Predictors of mortality have been identified in two US cohorts of SSc-PAH patients. The PHAROS registry found male gender, age > 60 years, New York Heart Association (NYHA) functional class IV, and DLCO < 39% predicted at the time of diagnosis were independent predictors of death [60]. Analysis of data from the REVEAL registry found older age, low systolic blood pressure, low 6-min walk distance (6MWD), elevated mean right atrial pressure, and high PVR to be unique predictors of mortality [7]. Additionally, a European study found that exercise hemodynamics, specifically exercise-induced increase in mPAP (hazard ratio (HR) 1.097, 95% CI 1.002–1.200) even after controlling for age, is associated with decreased transplant-free survival [61]. A previous systematic review and meta-analysis described the following features as predictive of mortality in patients with SSc-PAH: age at diagnosis, male sex, NYHA functional class, 6-min walk distance, DLCO, right atrial pressure, mPAP, cardiac index, PVR, SvO_2, and pericardial effusion [62]. A recent Australian prospective cohort study found the following factors to be predictive of mortality: older age at PAH diagnosis ($p = 0.03$), mild co-existent ILD ($p = 0.01$), worse WHO functional class ($p = 0.03$), higher mPAP at PAH diagnosis ($p = 0.001$), and digital ulcers ($p = 0.01$) [63]. Prior studies have shown NT-proBNP to be predictive of long-term survival; however, this was not confirmed in the PHAROS cohort [64, 65]. Although autoantibody status was not predictive of outcomes in the PHAROS cohort [34], U1RNP positivity has been associated with better survival in the UK cohort [66]. In a study of 70 patients with SSc-PAH, anti-AT1R levels above 15.8 units and anti-ETAR levels above 18.3 units predicted mortality better than some hemodynamic parameters including mPAP and PVR [46]. A retrospective study from one large US academic hospital included 286 SSc patients and data from their 6MWT to develop a scoring system to predict mortality in SSc-PAH [67]. The scoring is comprised of distance walked in 6 min, Borg dyspnea index and saturation of oxygen at 6 min (DIBOSA). The DIBOSA score in these patients correlated with mPAP ($R = 0.454$, $p < 0.0001$) and negatively correlated with 3-year survival ($r = -0.922$, $p < 0.0001$). The 3-year survival rates for DIBOSA scores of 0, 1, 2, and 3 were 100, 100, 88, and 67%, respectively.

Treatment

Current treatment algorithms recommend treating patients with NYHA functional class II or higher. The primary goal of treatment is to improve functional status. Many medications have been studied and approved for use in PAH including for patients with SSc-PAH.

Phosphodiesterase 5 (PDE-5) inhibitors (sildenafil and tadalafil) result in vasodilation via the cyclic guanosine monophosphate/nitric oxide (cGMP-NO) pathway and

additionally have antiproliferative effects. They are oral medications and are generally well tolerated. Sildenafil has been studied in IPAH and CTD-PAH [68, 69] and has been shown to improve functional status. It is approved at a dose of 20 mg three times daily. Tadalafil has been studied in a randomized trial of IPAH and associated PAH (APAH) [70] and showed improved exercise tolerance and quality of life as well as reduced clinical worsening. Tadalafil is approved for 40 mg once daily dosing.

Riociguat, a soluble guanylate cyclase stimulator, also works via the cGMP-NO pathway by stimulating guanylate cyclase and increasing cGMP production. It is an oral medication dosed from 0.5–2.5 mg three times daily. A subgroup analysis of CTD-PAH patients from the PATENT-1 and PATENT-2 studies showed that riociguat was well tolerated and led to improvement in 6MWD, WHO functional class and hemodynamic parameters including PVR and CI [71].

The endothelin receptor antagonists (ERA) are bosentan, ambrisentan and macitentan. They have been shown to improve exercise tolerance and hemodynamics in PAH patients [72–74]. Bosentan, a dual receptor antagonist (endothelin receptor type A (ET_A) and endothelin receptor type B (ET_B)), was the first to be approved for the treatment of PAH and is a twice daily oral medication with a relatively high incidence of liver function test abnormalities. Ambrisentan is a once daily ERA with higher specificity for the ET_A receptor. Macitentan is a once daily dual receptor antagonist which was the first PAH-specific therapy to show reduced mortality in patients with PAH [73].

Prostacyclins (epoprostenol, iloprost, and treprostinil) are powerful pulmonary vasodilators with antiproliferative and antiplatelet effects. Epoprostenol is a continuous IV infusion that showed improved exercise capacity, functional class, and hemodynamics in a randomized trial of 111 SSc-PAH patients [75]. Iloprost is available as inhaled and intravenous (in EU) formulations. RCTs have shown improved exercise tolerance using inhaled iloprost alone [76] and improved exercise tolerance and functional class when iloprost was combined with bosentan [77]. Treprostinil is available as a continuous subcutaneous or intravenous infusion as well as inhaled and oral forms. A randomized trial of continuous subcutaneous treprostinil in 470 PAH patients (including 17% CTD-PAH) showed improved exercise tolerance, dyspnea indices, and hemodynamics [78, 79]. Selexipag is an oral prostacyclin receptor agonist. In a subgroup analysis of CTD-PAH patients from the GRIPHON study, selexipag delayed disease progression of PAH (defined as a reduction in functional capacity or need for additional therapy) and was well tolerated [80].

Combination therapy has been described in multiple studies. The AMBITION study showed improved outcomes for patients started on up-front therapy with ambrisentan and tadalafil compared to either therapy alone, with results confirmed in a subgroup analysis in CTD-PAH and SSc-PAH patients [81, 82••]. Hassoun et al. similarly showed significantly improved hemodynamics, RV structure and function, and functional status in treatment naive SSc-PAH patients treated with up-front oral combination therapy [83]. Additionally, the PHAROS registry showed a faster time to clinical worsening in patients whose initial therapy was an ERA alone compared to initial therapy with PDE-5 inhibitors or ERA/PDE-5 inhibitors in combination [84]. Combination PAH therapy, which was defined as treatment with more than one agent from any of the three classes (ERA, PDE5i, prostacyclin analogues), was also shown to be a predictor of survival in two different Australian studies [63, 85].

Anticoagulation is a controversial topic with regards to SSc-PAH. Though non-CTD-PAH patients have been shown to benefit from anticoagulation, some studies have shown worse outcomes in SSc-PAH patients who were given warfarin compared to those who were not anticoagulated [86, 87]. Alternatively, a prospective cohort study of 117 Australian CTD-PAH patients (the majority of whom had SSc-PAH) demonstrated that warfarin was an independent predictor of survival [85]. Another Australian cohort study of 132 SSc-PAH patients showed that anticoagulation, compared to no anticoagulation conferred a survival advantage with a mean time to death of 5.4 ± 2.5 years vs. 3.5 ± 2.1 years ($p = 0.001$) [63]. Further study of anticoagulation in SSc-PAH is necessary. A multicenter Australian RCT comparing apixaban to placebo in SSc-PAH patients over 3 years in addition to oral PAH therapy is planned [88].

Exercise training may be another important adjunctive therapy for PAH. A small study evaluated 15 weeks of exercise therapy, which involved at least 5 days per week of bicycle, dumbbell and respiratory therapy, in addition to medical therapy for 21 patients with CTD-PAH (9 with SSc-PAH). Nine patients were WHO functional class II, 7 were class III and 5 were class IV. At follow-up, patients demonstrated improved exercise tolerance, quality of life, and hemodynamic parameters. Additionally, these patients had excellent 1-, 2-, and 3-year survival rates (100%, 100% and 73%, respectively) [89]. Since this study was small and uncontrolled, exercise therapy may not be appropriate for all patients with SSc-PAH and larger studies are necessary to confirm these results.

Finally, lung transplant is an option for patients with SSc and end stage lung disease. Patients with SSc may not be considered candidates for lung transplantation at certain centers due to concerns of esophageal disease leading to potential increased risk of aspiration and ultimately graft failure. However, more recent studies show a similar survival in patients with SSc-PAH who underwent lung transplantation compared to patients with other lung transplant indications, including IPAH and idiopathic pulmonary fibrosis [90, 91]. A systematic review of seven observational studies evaluating post-transplant survival concluded that SSc-PAH patients had 1-, 2-, and 3-year survival rates of 59–93%, 49–80%,

and 46–79%, respectively, which is similar to survival rates of patients with IPAH and idiopathic pulmonary fibrosis requiring lung transplantation [92]. A retrospective nationwide study of 229 adults with SSc, 201 with PAH, and 3333 with ILD who underwent lung transplantation in the US between 2005 and 2012 concluded that a diagnosis of SSc did not confer an increased risk of death at 1 year when compared with PAH not associated with SSc (HR 0.85 [95% CI 0.50–1.44]) [93].

Conclusions

In summary, PAH is a leading cause of morbidity and mortality in SSc. Several clinical, laboratory and hemodynamic factors predict mortality in SSc-PAH. Screening algorithms have been developed to enhance earlier detection and treatment of PAH in SSc patients. Although many treatment modalities including medications and transplantation are available for the management of SSc-PAH, survival rates remain poor. The institution of early, up-front combination therapy may improve outcomes in these patients.

Compliance with Ethical Standards

Conflict of Interest Dr. Chung reports grants from United Therapeutics, personal fees from Third Rock Venture, Reata, Gilead, and Actelion, outside the submitted work.

Dr. Sundaram has no conflicts to disclose.

Human and Animal Rights and Informed Consent Human and Animal Rights: All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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