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Pulmonary Hypertension in Systemic Sclerosis: *An Update on Clinical and Serologic Features, Screening, and Management*

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Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease with the highest case-specific mortality of the autoimmune illness.[1] The most common causes of SSc-related death are pulmonary hypertension and interstitial lung disease (ILD).[2] In total, these two complications account for over half of SSc-related deaths. It has been well recognized that pulmonary arterial hypertension (PAH) in SSc patients portends a worse prognosis than PAH from other causes.[3,4] Although survival in SSc-related PAH has improved[5-7] with modern therapeutics, as we will discuss below, SSc-PAH survival still lags behind that of survival with PAH from other causes. It has been shown that systematic pulmonary hypertension (PH) screening programs in SSc are associated with better survival,[8] likely due to earlier detection and intervention. This highlights the need for rheumatologists to maintain a high clinical suspicion for pulmonary hypertension and appropriately screen their SSc patients for the presence of this complication.

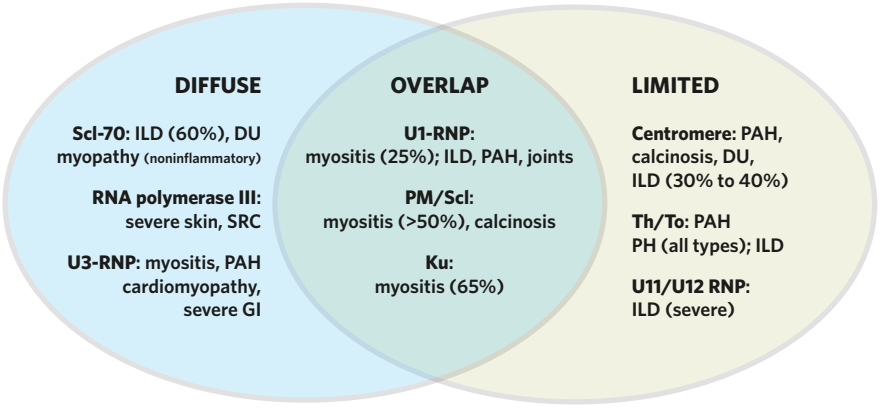
The objective of this article is to review the characteristics and risk factors for developing SSc-related pulmonary hypertension, and provide an update on approaches to targeted screening and treatment.

Systemic Sclerosis and Pulmonary Hypertension

SSc is a heterogeneous disease with some patients experiencing a very benign course, while others experience rapidly progressive or fatal disease. SSc is divided into two clinical subtypes based on the extent of skin thickening and distinct differences in natural history. These subtypes are: 1) diffuse cutaneous SSc with rapidly progressive and widespread (diffuse) skin thickening proximal to the elbows or knees, characterized by early internal organ involvement, and 2) limited cutaneous SSc with slowly or nonprogressive skin thickening restricted to the face and distal extremities, typified by slow accumulation of organ manifestations. Both diffuse and limited SSc patients can develop pulmonary hypertension, although PAH is more frequent in limited SSc patients.

SSc pathogenesis is characterized by the complex interplay of vascular injury with resultant vasculopathy, immune system activation, and fibrosis. Raynaud's phenomenon is the most common initial symptom of SSc, suggesting that peripheral vascular involvement occurs early in the disease. Pulmonary arterial hypertension is most often a later complication in SSc, developing years or decades after the first SSc symptom. This highlights the importance of risk factor assessment and targeted pulmonary hypertension screening throughout the lifetime of the SSc patient.

Figure 1. Cutaneous and Internal Organ Associations of SSc Autoantibodies



ILD = interstitial lung disease; **DU** = digital ulcers; **SRC** = scleroderma renal crisis; **PH** = pulmonary hypertension; **PAH** = pulmonary arterial hypertension

Classification of Pulmonary Hypertension

Pulmonary hypertension has been classified by the World Health Organization (WHO) into five groups, as depicted in Figure 1. *Uniquely, SSc patients can be afflicted with three different types of pulmonary hypertension: Group 1, due to obliterative vasculopathy, is the most common in SSc patients and is referred to as PAH.* The next most common subtype found in SSc is WHO Group 3 (PH related to ILD), and then Group 2 (pulmonary venous hypertension due to cardiac dysfunction). Because the therapy for PH differs amongst the WHO Groups, it is important that the specific group be delineated. Occasionally a patient will have features of more than one WHO Group.

Pulmonary hypertension is a hemodynamically defined entity. In general, PH is defined as a resting mean pulmonary artery pressure (mPAP) ≥ 25 mmHg on right heart catheterization (RHC).[9] Further discrimination of WHO Groups is defined below, and depicted in Table 1.

WHO Group 1 PAH

The classic hemodynamic definition for precapillary pulmonary arterial hypertension is a resting mPAP ≥ 25 mmHg **and** a pulmonary artery wedge pressure (PAWP) of < 15 mmHg on right heart.[10] PAH is characterized by a progressive increase in pulmonary vascular resistance, which can result in right ventricular failure and death.[11] Vascular injury occurs early, mostly involving arterioles, and precedes fibrosis.[12] The latter results in concentric obliterative lesions,[13] which likely represent a continuum of changes due to adaptive angiogenesis.[13,14] This is the population for whom FDA-approved vasodilators are available for treatment.

WHO Group 2

Postcapillary pulmonary venous hypertension is defined as a resting mPAP of ≥ 25 mmHg **and** a PAWP of > 15 mmHg, which may be due to

Table 1. WHO Clinical Classification of Pulmonary Hypertension

Group 1	**Pulmonary arterial hypertension**, related to connective tissue disease, (including SSc, mixed connective tissue disease or lupus); human immunodeficiency; idiopathic pulmonary arterial hypertension; portopulmonary hypertension; heritable pulmonary hypertension; pulmonary hypertension related to drugs/toxins; and idiopathic pulmonary hypertension
Group 2	Pulmonary hypertension **related to left heart disease**, including diastolic dysfunction, valve disease, or reduced ejection fraction
Group 3	Pulmonary hypertension **related to lung disease**, including COPD/emphysema, interstitial lung disease, sleep disordered breathing
Group 4	Pulmonary hypertension **related to chronic pulmonary emboli**
Group 5	**Miscellaneous** pulmonary hypertension

left ventricular disease (systolic or diastolic dysfunction) or valvular disease (mitral or aortic). The SSc population tends to have more left ventricular dysfunction compared to those with idiopathic pulmonary arterial hypertension with similar hemodynamics. These SSc patients do not have a significantly increased mortality.[15] Patients with pure Group 2 pulmonary hypertension are not eligible for PH-specific therapies.

WHO Group 3

Patients with SSc and various forms of ILD are at risk to develop pulmonary hypertension. Therapy for this population is controversial, depending on the severity of the ILD. Utilizing pulmonary function test (PFT) values with a ratio of FVC%/DLco% > 1.6 may identify SSc patients with significant pulmonary vascular disease.[16,17] Initiation of PAH-specific therapies in this population could result in deterioration of oxygenation due to ventilation-perfusion mismatching.[18]

PH Severity

The severity of pulmonary hypertension is determined by invasive hemodynamics and right ventricular dysfunction. Exertional capacity utilizing the WHO Functional Classification (modeled after the NYHA Functional Classification) can help establish patient disability (Table 2).

Exercise-induced Pulmonary Arterial Hypertension

In the mid-2000s, it was recognized that there might be less severe degrees of pulmonary vascular disease, resulting in elevated pulmonary artery pressure with exercise but not at rest,[19] that may precede the development of pulmonary hypertension in some patients. This stage is termed exercise-induced pulmonary hypertension.[16] The original definition of exercise-associated PAH was an increase of the mPAP of > 30 mmHg with exercise on RHC. This specific requirement has been eliminated from current diagnostic criteria due to a lack of consensus on the cut-off values to define normal, as well as the type of exercise performed and patient position during testing. An increase in pulmonary artery pressure out of proportion to cardiac output with exercise likely represents evidence of early pulmonary vascular disease. Detection of patients with early pulmonary vascular disease identifies patients for closer monitoring for the development of resting pulmonary arterial hypertension, or more controversially, early treatment with pulmonary vascular-specific therapies.

Epidemiology of SSc and PAH

SSc is an uncommon disease, with a prevalence of 240 per million in the United States.[20] While the incidence and

Table 2. WHO Classification of Functional Status in Pulmonary Hypertension

Class	Description
I	**No limitation of usual activity** Ordinary physical activity does not cause fatigue, dyspnea, chest pain, or presyncope
II	**Mild limitation of physical activity** Comfortable at rest, but normal physical activity causes increased fatigue, dyspnea, chest pain, or presyncope
III	**Marked limitation of physical activity** Comfortable at rest, but less than ordinary activity causes fatigue, shortness of breath, chest pain, or presyncope
IV	**Unable to perform physical activity, is uncomfortable at rest or has signs of right heart failure** Shortness of breath and fatigue may be present at rest, and symptoms are increased by almost any physical activity

prevalence varies throughout the world, the United States is recognized to have the highest of both. The exact prevalence of pulmonary hypertension (regardless of subtype) in SSc is unclear, with estimates ranging from 10% to 20% in observational cohort studies. The prevalence of Group 1, or PAH, is approximately 10% to 15%, based on observational studies.[21-25] As an example of an American cohort, UPMC and the University of Pittsburgh Scleroderma Center prospectively followed > 1100 SSc patients between 2000 and 2010 (unpublished data). Of these, 17% developed PH (10% Group 1, 2% Group 2, and 5% Group 3).

In striking contrast to the SSc population, the prevalence of PAH is 15 to 50 cases per million, or 0.00005% in the general population.[17,26,27] This contrasts drastically with the 8% to 15% in the SSc population.[2]

Mortality in SSc-PAH: PAH has emerged as a significant cause of morbidity and mortality in the SSc population. Nearly one-third of patients diagnosed with PAH die of PAH.

This greatly increased risk of developing PAH, combined with the poor survival in SSc, underlies the importance of screening for PAH in SSc.

Symptoms and Diagnosis of Pulmonary Hypertension

Symptoms

Symptoms of pulmonary hypertension are nonspecific, contributing to a delay in diagnosis for some patients. The most common complaints elicited are dyspnea, exercise intolerance, fatigue, and presyncope; the latter is a poor prognostic sign. These nonspecific symptoms are attributed to impaired transport of oxygen and decreased cardiac output. With advanced disease there may be angina-like chest pain due to right ventricular ischemia.

Diagnosis

The diagnosis of pulmonary hypertension can only be made by the gold standard of right heart catheterization. Patients who are suspected to have PAH based upon clinical presentation and noninvasive testing should be referred to either a cardiologist or a pulmonologist who specializes in pulmonary hypertension, who may ultimately perform RHC. The specifics of RHC testing results by WHO Group are discussed below. RHC can determine the severity of PH based upon mean pulmonary artery pressure, as well as the presence (or absence) of left heart disease. Although the echocardiogram may be useful as an initial screening tool, it is not sufficient to diagnose pulmonary arterial hypertension as it may over or underestimate pulmonary pressures, especially in the presence of interstitial lung disease.[28]

Risk Factors for Developing PH in SSc

The vast majority of literature examining the risk factors for developing PH has been performed in prevalent cohorts, which generally contain larger numbers of limited SSc patients given the survival benefit of this disease subtype. Thus, we know much more about risk factors in limited SSc than in diffuse SSc. The study of prevalent cohorts may account for why anti-centromere antibody has been found to be a predictive factor for developing PH based on the frequency of this antibody in the general population; patients with other antibodies actually have greater rates of developing PH. This potential bias should be kept in mind when reviewing this section.

Identifiable risk factors for developing pulmonary hypertension in SSc include both demographic and SSc-specific characteristics. In several observational cohorts, older age and male gender[17,29,30] have been associated with an increased risk of developing PAH or Group 1 PH. Patients with ILD are at risk for developing Group 3 PH, and those with diastolic dysfunction or myocardial dysfunction are at risk to develop Group 2 PH. One Australian study found that patients with mild ILD were likely to develop PAH.[31]

SSc-specific Risk Factors for Developing Group 1 PAH

In multiple historical and contemporary studies, limited SSc has been shown to be a risk factor.[17,30,31] Older age at SSc onset[32,33] and longer disease duration[29] have also been identified as PAH risk factors. The latter has been demonstrated in meta-analyses.

A low DLco (< 75% predicted), progressive decline in DLco, and a high forced vital capacity (FVC)/DLco ratio (FVC/DLco > 1.6)[16,17,34] are established risk factors. These associations likely reflect the evolving underlying pathophysiology.

PFT abnormalities provide rheumatologists the ability to subset higher risk patients who may need referral for RHC. It also provides strong rationale to use PFTs to screen for both ILD and PH.

Serologic SSc Testing and Pulmonary Hypertension

In recent years, the serologic (autoantibody) classification of SSc has been increasingly recognized to be beneficial in the prognosis and management of patients. There are 10 recognized SSc-associated autoantibodies. SSc patients rarely have more than one SSc-associated autoantibody. These autoantibodies are associated with both the cutaneous subtype of SSc and frequency of internal organ involvement, as depicted in Figure 1 on Page 2.

There are four primary SSc-related antibodies that have been associated with an increased risk for developing Group 1 PAH. These antibodies include anticentromere,[35] anti-Th/To,[36,37] anti-U3RNP,[38] and anti-U1RNP. Anti-U3RNP and anti-Th/To antibodies remain difficult to reliably identify using commercial antibody testing, but both are associated with nucleolar staining on routine ANA testing by immunofluorescence. Several studies have reported an increased risk of PAH in patients with nucleolar staining pattern,[39] most likely due to undetected anti-Th/To or anti-U3RNP antibodies. Patients with one of these four antibodies or a nucleolar pattern ANA test result should be routinely questioned for PAH-related symptoms and undergo routine screening. Not surprisingly, patients with Scl-70 antibodies (which carry a high risk of ILD) are more likely to develop SSc-PH Group 3.

Screening for PAH in SSc: There Remains Room for Improvement

Patients with SSc are 10,000 times more likely to develop PAH than the general population. Given the lifetime risk of pulmonary hypertension, combined with the nonspecific symptoms and poor survival in untreated disease, there is strong rationale for screening SSc patients for pulmonary hypertension.

Greater than two-thirds of SSc-PAH patients present with advanced PAH (WHO Functional Class III and IV rather than II).[40,41] There remains a delay in the diagnosis of PAH with a mean time from symptom onset to diagnosis of > 2 years (unchanged from previous NIH registry),[42] despite efforts to aggressively screen SSc patients. The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) demonstrated that there has not been a significant improvement in earlier diagnoses of PAH in patients with connective tissue disease.[43]

Objective Testing: Strengths and Pitfalls

Scleroderma patients have numerous problems that may cause exercise limitation and shortness of breath. These may include, but are not limited to, musculoskeletal pain, ILD, and PAH. Symptoms such as dyspnea are minimal or absent in 22% of patients with scleroderma-associated PAH.[44] Signs of pulmonary hypertension or right heart failure on physical examination, such as increased pulmonic heart sound, elevated jugular venous distention, or lower extremity edema, may confirm suspicions but are more likely present at later stages of disease. Other screening tools, such as electrocardiogram or chest radiography, are abnormal only after pulmonary artery pressures are elevated.

Echocardiogram

Doppler echocardiography (DE) is a common method used to identify elevated pulmonary artery pressure in patients with SSc. In symptomatic patients, DE has a sensitivity and specificity of 90% and 75%, respectively, for detecting moderate to severe elevation in pulmonary artery pressure.[45] Pulmonary hypertension is not as easily identified in asymptomatic SSc patients. A small DE study of 76 asymptomatic SSc patients showed a sensitivity and specificity of 72.7% and 88.2% for PH when patients had an estimated pulmonary artery systolic pressure (PASP) ≥ 40 mmHg. It is the recommendation from multiple societies that asymptomatic patients with the scleroderma spectrum of disease (defined as SSc, mixed connective tissue disease, or other connective tissue disease with prominent scleroderma features) undergo an annual screening to detect the presence of PAH.[9,46,47]

PFTs

In the absence of significant obstructive or ILD in SSc, a reduced DLco may indicate presence of pulmonary vascular disease. Due to the potential concomitant presence of ILD and pulmonary vascular disease, a low DLco% in relation to forced vital capacity (FVC%) may be indicative of prominent pulmonary vascular disease. A cutoff FVC%/DLco% ratio of 1.6 identifies patients with pulmonary vascular disease "out of proportion" to interstitial lung disease.

Screening Strategies for SSc-associated Pulmonary Hypertension

Consensus Recommendations for PAH Screening

There are multiple position papers by individual authors on screening for PAH in SSc patients. All agree that screening should occur at baseline and during follow-up.[9,10,47] Many recommend yearly echocardiograms (others every other year) and recognize the importance of PFTs as part of screening. Medical societies have developed expert opinions regarding screening. The American College of Chest Physicians states that in SSc patients, PFTs with DLco should be performed periodically (every 6 to 12 months) to improve detection of pulmonary vascular and interstitial lung disease.[9]

In 2013, the Scleroderma Foundation and the Pulmonary Hypertension Association published expert consensus recommendations developed using a multidisciplinary approach.[46] These recommendations are shown in Table 3. The key recommendation is that all SSc patients, or patients with mixed connective tissue disease with scleroderma spectrum features, should be screened for PH. Initial screening should include PFTs with DLco, echocardiogram, and measurement of NT-proBNP at baseline. The DETECT algorithm (next paragraph) may be applied to patients if the DLco < 60% and > 3 years of SSc symptoms. Right heart catheterization is mandatory for diagnosis.

The DETECT Algorithm

Coghlan and colleagues published a two-step, evidence-based algorithm to detect PAH in high-risk SSc population with DLco < 60%.[48] The DETECT study allocated points depending on the presence of risk-factors for PAH. In Step 1, nonechocardiographic variables, including the FVC/DLco ratio, the presence of telangiectasias or anticentromere antibody, high uric acid or NT-proBNP, and right axis deviation on EKG, are added together to determine if an echocardiogram should be performed. Step 2 combines points accrued from echocardiographic variables (right atrial area and tricuspid regurgitant jet velocity) with points from Step 1 to determine if RHC should be performed. The primary analysis resulted in an overall sensitivity and specificity of 96% and 48%, respectively. Caution should be used in applying the DETECT algorithm, keeping in mind that it was developed using a high-risk patient population with a DLco < 60% and has not been validated in the general SSc population. The web page (http://detect-pah.com) does not allow U.S. residents to use the calculator.

Table 3. Recommendations for Pulmonary Hypertension Screening

Initial visit	PFTs with DLco, echocardiogram, NT-proBNP, and DETECT algorithm if appropriate. All have moderate to high quality evidence to support application.
Follow-up	• Echocardiogram if new signs or symptoms develop (high quality) • Annual PFTs with DLco and transthoracic echocardiography/ echocardiogram (TTE) are commonly done, although evidence is lower in quality. ***We typically perform each every other year in most SSc patients.*** • Yearly echocardiograms in high-risk patients (anti-Th/To). ***We typically alternate PFTs and TTE each year in most SSc patients.*** • NT-proBNP if new signs or symptoms develop.
Refer for Right Heart Catheterization if any of the following are present:	• RVSP or estimated PA pressure U 45 mmHg • TR velocity of 2.5 to 2.8 m/s with symptoms of PH • TR velocity of > 2.8 m/s • FVC/DLco ratio > 1.6 and/or DLco < 60% • If the DETECT algorithm is met in patients with DLco < 60% and disease duration > 3 years

Referral for Right Heart Catheterization

We typically refer patients to our dedicated PH clinic if the echocardiogram reveals an estimated PASP of > 45mmHg or patients have dyspnea with an estimated PASP > 40mmHg. Expert consensus recommendations also suggest referral for

RHC if patients have a tricuspid regurgitant (TR) velocity of 2.5 to 2.8 with symptoms of PH, a TR velocity of > 2.8 m/s, FVC/DLco ratio > 1.6, and/or DLco < 60% or if they meet the DETECT criteria and DLco < 60% predicted and disease duration > 3 years.[46] Please refer to Table 3.

Exercise Testing to Identify PAH in SSc Patients[49]

Exercise-induced pulmonary arterial hypertension (ePAH) can be identified with exercise echocardiogram, but these findings need to be confirmed with exercise RHC.[16] SSc patients with normal resting pulmonary artery pressure and an excessive increase in pulmonary artery pressure with exercise are associated with subclinical right ventricular dysfunction and reduced survival.[50,51] The beneficial hemodynamic effects of PAH-specific therapy with the endothelin-receptor antagonist ambrisentan for SSc-ePAH has been demonstrated in a small prospective, single-center population of patients.[52] Diagnosis and therapy in this population should be reserved for an expert referral center, such as the Comprehensive Pulmonary Hypertension Program at UPMC.

PAH-specific Management

Referral

Once the diagnosis of PAH has been made or is suspected, it is important to refer the patient to a center specializing in pulmonary hypertension for additional testing and further care. Timely confirmation of PAH and institution of pharmacologic therapy improves cardiopulmonary hemodynamics and slows the progression of PAH severity.[40,53] In particular, SSc subjects with mild PAH (WHO Functional Class I and II) have improved survival when compared to those presenting with WHO Functional Class III and IV.[26] The EARLY trial convincingly demonstrated that WHO Functional Class II PAH subjects treated with PH-specific therapy, compared to placebo, had improved cardiopulmonary hemodynamics, no deterioration of functional class, and less PAH-associated clinical worsening.[40,53] If practitioners are unsure of the location of a dedicated PH Center, the Pulmonary Hypertension Association (PHAssociation.org) provides a list of physicians treating pulmonary hypertension. The PHA is currently instituting an accreditation process for dedicated comprehensive PH Centers that provide clinical care and research opportunities for patients (PHAssociation.org/PHCareCenters).

Pharmaceutical Management

In the last 20 years there has been an explosion of medications available for the treatment of PAH. Epoprostenol (Flolan) was approved in 1995 as the initial therapy. Now, there are 13 FDA-approved medications for the management of PAH (See Table 4 on Page 8). While initially medical management focused on add-on or step-up therapies, more recent studies have demonstrated that patients may benefit from up-front combination therapy.[53]

There are four major groups of PAH-specific therapies, which include: prostanoids, endothelin-receptor antagonists (ERAs), phosphodiesterase-5 (PDE-5) inhibitors, and soluble guanylate cyclase stimulators (SGC). All four groups are FDA-approved therapies for Group 1 PAH. The timing of the initiation can be described as monotherapy, sequential combination therapy (the addition of another agent after a period of time of monotherapy), or up-front combination therapy (the simultaneous initiation of two or more agents).

The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial demonstrated very exciting and landmark results. This study evaluated up-front combination therapy with simultaneous ambrisentan and tadalafil in drug naïve Group 1 PAH patients, compared to ambrisentan monotherapy and tadalafil monotherapy. This study included some patients with SSc-PAH,[53] on whom a post-hoc analysis was later performed and just recently published. The primary endpoint was time to clinical failure defined as death, first occurrence of hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. In the original AMBITION trial analysis of all Group 1 PAH patients, those receiving up-front combination therapy group (18%) reached the primary composite endpoint compared to 34% of the ambrisentan and 28% of the tadalafil monotherapy groups. This represents a 50% risk reduction in the first event of clinical failure by using up-front combination therapy. In the very interesting subgroup analysis of SSc-PAH patients (n=118), the initial combination reduced the risk of clinical failure by 44% (HR 0.44, 95% confidence interval 0.24 to 0.77). In the CTD population, the most common adverse event was peripheral edema, which was more frequent in the up-front combination therapy group in the CTD patients.[54]

Continued on Page 9

Table 4. FDA-approved Therapy Options for PAH

Drug Class	Drug	Mode of Administration	Indication	Side Effects
Prostacyclins	Epoprostenol (Flolan, Veletri)	IV	iPAH, HPAH, PAH-CTD WHO FC III, IV	Headache, jaw pain, flushing, nausea, joint or muscle pain, diarrhea
	Treprostinil (Remodulin)	SQ	iPAH, HPAH, congenital heart disease PAH, PAH-CTD WHO FC II-IV	Site irritation, headache, GI
	Treprostinil (Remodulin)	IV	iPAH, HPAH, congenital heart disease PAH, PAH-CTD WHO FC II-IV	Headache, jaw pain, flushing, GI, muscle pain
	Treprostinil (Tyvaso)	inhalation	PAH WHO FC III	Cough, headache, flushing, throat irritation
	Treprostinil (Orenitram)	oral	iPAH, HPAH, PAH-CTD WHO FC II, III	GI discomfort, diarrhea
	Iloprost (Ventavis)	inhalation	iPAH, HPAH, PAH-CTD WHO FC III-IV	Cough, headache, flushing, throat irritation
Selective IP Receptor Agonist	Selexipag (Uptravi)	oral	PAH WHO FC not specified	Headache, diarrhea, jaw pain, nausea, myalgias, vomiting, flushing, arthralgias, anemia, hyperthyroidism
Endothelin-receptor Antagonists (ERAs)	Bosentan (Tracleer)	oral	PAH WHO FC II-IV	Hepatotoxicity (LFT elevation > 3 times ULN in 11%), peripheral edema, anemia
	Ambrisentan	oral	iPAH, HPAH, PAH-CTD WHO FC II-III	Peripheral edema, nasal congestion, sinusitis, flushing, anemia requiring blood transfusion
	Macitentan	oral	PAH WHO FC not specified	Peripheral edema, nasopharyngitis, bronchitis, headache, anemia
PDE-5 Inhibitors	Sildenafil	oral	iPAH, PAH-CTD WHO FC II-III	Headache, dyspepsia, epistaxis, visual changes
	Sildenafil	IV	iPAH, PAH-CTD WHO FC II-III	Headache, flushing, site reaction
	Tadalafil	oral	iPAH, PAH-CTD WHO FC II-III	Headache, myalgia, flushing, dyspepsia, joint pain, visual changes
Guanylate Cyclase Stimulant	Riociguat	oral	PAH, CTEPH WHO FC not specified	Hypotension

Abbreviations: **iPAH** = idiopathic pulmonary arterial hypertension; **HPAH** = heritable PAH; **PAH-CTD** = PAH related to connective tissue disease; **CTEPH** = chronic thromboembolic pulmonary hypertension.

Continued from Page 7

Hassoun and colleagues at Johns Hopkins performed an investigator-initiated study using up-front combination of ambrisentan and tadalafil in WHO FC II and III PAH patients in a similar fashion to AMBITION.[55] Their analysis included the co-primary endpoints of right ventricle mass reduction by cardiac magnetic resonance imaging and decrease in PVR.[55] This multicenter, prospective, 36-week open-label trial of 24 treatment naïve scleroderma-associated PAH (SSc-PAH) patients demonstrated improvements in the co-primary endpoints. The subjects' exercise capacity and serum NT-proBNP was significantly improved.

Recently, a secondary analysis of the AMBITION study demonstrated that initial combination therapy might be associated with a survival advantage compared to initial monotherapy for newly diagnosed patients with PAH.[56] Finally, Coghlan and colleagues have shown that a subgroup analysis of the AMBITION trial that included 187 connective tissue disease-associated PAH (63% were SSc-PAH patients) had a 57% reduction in the relative risk of clinical failure in the combination therapy group compared to pooled monotherapy. The results were similar for the SSc-PAH subjects, who had a 56% reduction in the relative risk.[54] Interestingly, an observational study from the American-based Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry (PHAROS) cohort suggested that initial treatment combination therapy or initial treatment with a PDE5 inhibitor had a longer time to clinical worsening than patients treated with an ERA. However, this study was relatively small and observational, so limited conclusions can be drawn from it.[5]

The most recent publication to report on the effect of PAH therapy in the SSc population was a subgroup analysis of the riociguat[59] trial PATENT-1, and the open-label extension trial, PATENT-2. 443 patients were randomized in PATENT-1, of which 111 had connective tissue disease (CTD) with 66 having SSc. Patients with CTD had improvement in 6MWD, similar to non-CTD patients with PAH (+18 m with riociguat, -8 m with placebo). Patients with SSc treated with riociguat had maintenance of their 6MWD (+4 m), while patients on placebo had a decline in their 6MWD (-37 m). This suggested that riociguat may prevent worsening of 6MWD. Adverse events were similar in the CTD and non-CTD patients. The 2-year survival rate in PATENT-2 was similar for patients with SSC and those with idiopathic/familial PAH and CTD-related PAH.

A separate study (NCT 02283762) is underway in patients with early diffuse SSc investigating the potential effect of riociguat on skin fibrosis.

Nonpharmaceutical Evaluation and Management

Nonpharmaceutical management continues to play a vital role in the management of pulmonary hypertension of all subtypes. Nonpharmaceutical management includes oxygen therapy, as well as exercise including formal pulmonary rehabilitation programs. As hypoxia can drive the underlying pathologic progression in pulmonary hypertension, it is important that patients be evaluated for the need for supplemental oxygen therapy with exercise desaturation tests. If patients are reporting increased dyspnea, a repeat exercise desaturation test should be considered as patient oxygen needs can increase over time.

Outcomes

Outcomes for SSc patients with PAH have been shown to improve in the setting of modern therapies, although they still lag behind survival in those without SSc. The REVEAL registry showed that 3-year survival in newly diagnosed SSc-PAH was 51%, compared to 76% in those without an autoimmune illness.[57] The PHAROS investigators reported 1, 3, and 5-year survival rates as 95%, 76%, and 64%, respectively. The majority of deaths (60%) in the short-term were due to PAH. At 8 years of follow-up, survival was 50%, but most causes of death were unrelated to SSc.[58] PHAROS predictors of mortality included very low DLco (< 39% predicted) and Functional Class IV. Predictors of mortality in the REVEAL registry were older age, lower blood pressure, low 6 minute-walk distance (6MWD) < 165 m, and elevated pulmonary vascular resistance (PVR) > 32 Woods units.

Conclusion

Systemic sclerosis is a patient population at particularly high risk for developing pulmonary arterial hypertension. Scleroderma patients should be routinely screened for pulmonary arterial hypertension. Initial screening evaluation should include baseline measurements of PFTs with DLco, echocardiogram, and serum NT-proBNP. At-risk patients with a high probability for PAH should be referred to an expert center experienced in diagnosis and management of PAH, which can be identified on the PHA website. The gold standard for diagnosis of PAH remains right heart catheterization. Significant advances have been made in the pharmaceutical management of SSc-PAH, with evidence mounting for the use of up-front combination medication management.

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