REGULAR ARTICLE

Connective Tissue Disease, Interstitial Lung Disease, and Pulmonary Hypertension (CTD PH-ILD): A Distinct Entity and Potential Opportunity

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Connective tissue diseases are a multisystem disorder that can cause impairments in quality of life, shorten life expectancy, and increase the risk of mortality at a younger age. These patients have an increased risk for the development of pulmonary hypertension through several mechanisms including pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease. This review aims to discuss the various presentations of connective tissue disease associated with pulmonary hypertension associated with interstitial lung disease, demographics, and survival. It gives an overview of accepted mechanisms of disease pathogenesis, discusses advances in diagnostics, and treatment options. Despite a deeper understanding of disease pathogenesis, treatment for this remains limited to prevention of disease progression. The identification of the primary disease driver requires careful evaluation of the disease phenotype and is a potential target for treatment and prevention of death.

INTRODUCTION

Lung involvement in connective tissue disease (CTD) most commonly occurs as interstitial lung disease (ILD), pulmonary hypertension (PH), or a combination of both (PH-ILD). In most CTDs, including rheumatoid arthritis, systemic lupus erythematosus, polymyositis or dermatomyositis, Sjogren syndrome, mixed connective tissue disease, and systemic sclerosis (SSc), ILD is often early in the disease course and can be a presenting manifestation.[1] PH, on the other hand, can result from processes that affect organs other than the pulmonary vessels, such as left heart disease, liver fibrosis, and kidney dysfunction. CTD can also increase the risk of pulmonary emboli causing vascular remodeling due to endothelial damage without explicit venous thromboemboli.[2] More commonly, ILD causing hypoxic vasoconstriction and pulmonary arterial hypertension (PAH) due to a small vessel vasculopathy are the predominant causes of PH in CTD.[3] CTD-PH may therefore develop either as a consequence of progressive ILD or as an unfortunate complication of the autoimmune disease process itself. On a molecular level, this setting is a fraught with inflammatory cells including granulomas, myofibroblast, and extracellular matrix populations.[4] Altogether, this leads to a chronic inflammatory process that destroys functional lung parenchyma, encourages collagen deposition, and ultimately leads to fibrosis and an increased risk for morbidity and mortality.[5] The focus of this review is to understand the recent changes in defining CTD-PH-ILD, understand the pathophysiologic mechanisms involved, provide an approach to diagnosing the underlying phenotype, and offer new insights in considering treatment in the proper context.

DEFINITION, EPIDEMIOLOGY, AND PREVALENCE

The 6th World Symposium for PH revised the definition of group 3 PH in 2018. It requires a chronic a lung disease (CLD) accompanied by hemodynamic measurements via right heart catheterization (RHC). Hemodynamics must demonstrate a resting mean pulmonary artery pressure (mPAP) ≥ 20 mm Hg, PVR ≥ 3 Wood units, and a pulmonary artery occlusion pressure ≤15 mm Hg.[6] It is considered severe at mPAP ≥ 35 or at mPAP ≥ 25 mm Hg with cardiac index ≤ 2.0 L/min/m^2. Two studies in scleroderma patients demonstrated the importance of including what was previously thought of as *borderline PH*. They noted that a third of scleroderma patients with mPAP > 20 progressed to mPAP ≥ 25 in 3 years[7] with a mortality of 18%.[8] (Table 1)

Prevalence of ILD and PH-ILD in Connective Tissue Diseases (World Health Organization Group 3 PH)

The most common CTDs that present with group 3 PH-ILD are SSc, mixed CTD, sarcoidosis, and idiopathic inflammatory myositis.[4,9] The widespread variation in prevalence is because of the diagnostic techniques used to define PH and/or ILD. Furthermore, there are concomitant and multifactorial mechanisms leading to PH, and many of the studies diagnosed PH patients without RHC and through doppler echocar-

Key Words—pulmonary hypertension, interstitial lung disease, connective tissue disorders, vasodilators, immunosuppressants, detection of PH-ILD
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Table 1. PH in the Context of CLD PH[6]: (6th WSPH)

1. CLD without PH: mPAP < 21 mm Hg, or mPAP 21-24 mm Hg with PVR < 3 WU
2. CLD with PH: mPAP 21-24 mm Hg with PVR ≥ 3 WU, or mPAP 25-34 mm Hg
3. CLD with severe PH: mPAP ≥ 35 mm Hg, or mPAP ≥ 25 mm Hg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$)

Abbreviations: CLD, chronic lung disease; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WSPH, World Symposium for Pulmonary Hypertension; WU, Wood units.

diography with the exception of SSc. (Table 2)

Sarcoidosis is a granulomatous disease that appears with CTD and can present with multiple mechanisms leading to PH. Prevalence of PH in sarcoidosis ranges from 5.7% to 74% with a 5-year survival of 50% to 60%.[20] It is important to note that in studies with PH-ILD, sarcoidosis is often excluded and assigned to World Health Organization (WHO) group 5. Despite extensive fibrosis seen in 20% of sarcoidosis patients,[21] the PH in sarcoidosis is multifactorial (extrinsic pulmonary artery [PA] compression from lymphadenopathy, mediastinal fibrosis, pulmonary vascular arterial and venous granulomas, fibrosis-associated remodeling and obliteration of pulmonary vessels hypoxia, heart disease from granulomatous infiltration/cardiomyopathy from ectopy, and portopulmonary hypertension). Clinicians applying outcomes in trials with sarcoidosis-associated PH should be mindful of this fact.[22]

SURVIVAL: PH-ILD WITH THE WORST PROGNOSIS

Despite seemingly similar presentations, CTD-ILD differs in both response to treatment and prognosis from other forms of ILD such as idiopathic pulmonary fibrosis (IPF).[1] Furthermore, with PH onset regardless of cause of the PH, there is a trend toward increasing mortality in CTD with an estimated 3-year survival rate of 56%.[15] PH and/or ILD account for 60% of deaths in SSc.[23]

In the PHAROS registry (PH Assessment and Recognition of Outcomes in Scleroderma), SSc-PAH populations are found to have poorer long-term survival despite access to vasodilator therapy.[24] These worsen once CTD patients with ILD develop PH (CTD-PH-ILD). Data coming from SSc cohorts by Mathai and colleagues revealed that SSc patients with PH-ILD had an increased risk of death (hazard ratio 2.87) with 1-year, 2-year, and 3-year survival rates of 82%, 46%, and 39%. This is 5 times worse than survival in SSc or PH alone.[25] A lower diffusing capacity for carbon monoxide (Dlco) was associated with increased mortality, and there existed a trend toward decreased survival with higher PVRs.[25]

When authors explored the subsets of hemodynamics, they found that a low cardiac index was a marker for mortality in SSc-PAH patients while it was an increased mPAP for PH-ILD. This suggests that SSc-PH-ILD patients have increased risk of mortality earlier in the course of their disease when their mPAP starts to rise. This is echoed in studies looking at other CTDs with PH-ILD (rheumatoid arthritis, primary Sjogren, dermatomyositis/polymyositis, SSc) where patients with a higher mPAP at the initial evaluation had a worse survival regardless of the type of CTD.[26]

The French Network for PAH and the French Network for Rare Pulmonary Diseases (OrphaLung) reviewed 128 patients from 15 centers and found that at less severe hemodynamics, PVR ≈ 5 vs 8 Wood units ($P = .0005$) and lower Dlco (median 25% [interquartile range (IQR) 18%, 35%] versus 40% [IQR 31%, 51%]; $P = .0005$), mortality and WHO functional class was worse in those with SSc-PH-ILD than PAH.[27] Also, SSc-PH-ILD patients were younger and more regularly required continuous oxygen therapy.

Interestingly, the investigators found no difference in the initiation of oxygen therapy between SSc-PAH and SSc PH-ILD on PAH-specific therapy, although this study was not designed to distinguish between effects observed because of PAH-specific treatment versus worsening ILD.

Approach to Understanding the Spectrum of PH-ILD in Connective Tissue Disease

CTD-related PH (CTD-PH) occurs as a result of simultaneous mechanisms.[20] Lung predominant CTD with PH (CTD-PH-ILD) is therefore challenging to treat but presents a unique opportunity as these patients have a chance at responding to PH-targeted therapies.

Many believe that there are clear distinct phenotypes that drive the responsiveness to pulmonary vasodilator therapies in both PH-ILD and CTD-PH-ILD. In the group 3 phenotype, one is distinctly driven by hypoxic pulmo-

Table 2. Prevalence of PH-ILD and ILD in CTD

CTD	PH-ILD prevalence (%)	ILD prevalence (%)
SSc-ILD[a,b,c,d]	24[10]	70-90[11] (only 30-40 will develop clinically significant disease[12])
MCTD-ILD[a,b]	2-24[13]	20-78[2]
SLE-ILD[a,b]	<5[14]	1-15[15]
IIM[b]	7,9[16]	20-40[17]
RA-ILD[b]	<10[4]	6.5-33[18]
Sjogren	-	28-61[19]

Abbreviations: CTD, connective tissue disease; IIM, idiopathic inflammatory myositis (includes antisynthetase syndromes); ILD, interstitial lung disease; MCTD-ILD, mixed connective tissue disease associated with ILD; RA-ILD, rheumatoid arthritis associated with ILD; SLE-ILD, systemic lupus erythematosus associated with ILD; SSc-ILD, systemic sclerosis associated with ILD.

[a]World Health Organization Group 1.
[b]World Health Organization Group 2.
[c]World Health Organization Group 4.
[d]World Health Organization Group 5.

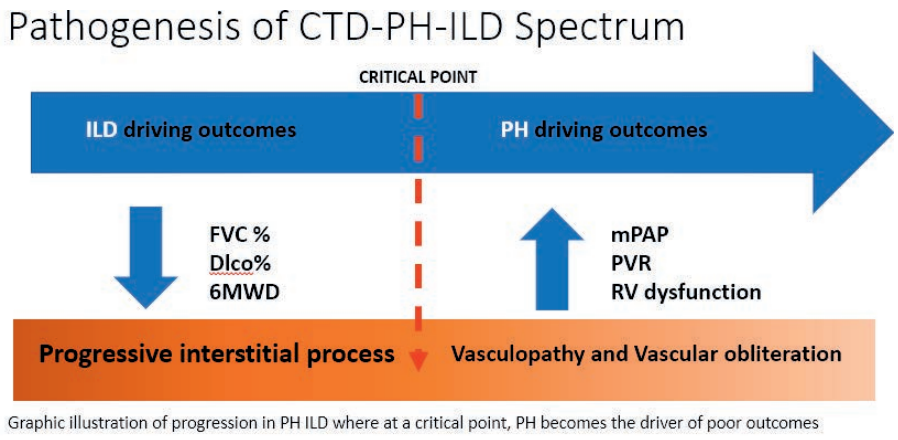

Figure: Pathogenesis of connective tissue disease and pulmonary hypertension associated with interstitial lung disease spectrum. Graphic illustration of progression in pulmonary hypertension associated with interstitial lung disease where at a critical point, pulmonary hypertension becomes the driver of poor outcomes. Adapted from King and Nathan.[20]

nary vasoconstriction versus a more hemodynamically/right ventricle (RV) failure group 1 phenotype.[20] There develops a critical point at which PH becomes the larger driver of outcomes, and this is probably more true and possibly earlier realized in CTD patients. King and Shlobin[28] offers a therapeutic approach to PH-ILD where one can view PH as a surrogate marker of disease progression in advanced fibrotic lung disease versus a maladaptive phenotype where PH is the driver of pathophysiologic derangements that is out of proportion to the degree of ILD. This maladaptive or out-of-proportion PH-ILD is thus more likely to benefit from the initiation of vasodilator therapy. (See Figure)

NONINVASIVE CLUES SUGGESTING PULMONARY VASCULAR DISEASE IN CTD-ILD

Clinical History and Examination

Patients with CTD-ILD-PH are more likely to be younger, female, and nonsmokers. Patients with preexisting ILD will endorse worsening exertional dyspnea or poor exercise capacity despite mild lung disease or severe lung disease that has been stable for several years. Patients will start to complain of symptoms suggestive of right heart dysfunction such as lower extremity, ascites, and weight gain. They often have rapid desaturations on activity with movement or mild exercise. Clinical high-risk features include syncope and presyncope, lightheadedness, dizziness, and kidney or liver dysfunction, which are suggestive of worsening cardiac output.

BNP or NT-proBNP

An elevated BNP (brain natriuretic peptide) or NT-proBNP (N-terminal-pro hormone BNP) are released in response to myocardial stretch, and serial levels can be used to prognosticate as they correlate with PVR and inversely correlate with 6-minute walk distance (6MWD). CTD patients with NT-proBNP levels of 395 pg/mL predicted PH with a 56% sensitivity 95% specificity.[1]

Pulmonary Function Testing

A 6-minute walk test has several variables that may help predict PH. A sudden decrease in walk distance and pronounced desaturation (distance-desaturation product) are both associated with PH and reduced survival.[29]

The DIBOSA is a composite score that includes 3 variables obtained from a 6-minute walk (DIstance walked in 6 min, BOrg dyspnea index, and SAturation of oxygen at 6 min). This was validated in cohort of more than 200 SSc patients diagnosed with a RHC. A score of 0 had a negative predictive value (NPV) of 100% and a score of 3 had a positive predictive value (PPV) of 86.58%. The DIBOSA score was devised as is a noninvasive way of predicting mPAP as measured by RHC and right ventricular systolic pressure (RVSP) as estimated by echocardiogram. It is a good predictor of disease severity and mortality and can be used to prognosticate SSc patients who are at risk for developing PH though could not distinguish between PAH (WHO group 1) and PH-ILD (WHO group 3).[30]

Other clues that patients are developing worsening cardiac dysfunction in the setting of CTD-ILD include a failure of the heart rate to fall after cessation of exertion (abnormal heart rate recovery) of >13 b/min.[31]

Pulmonary hemodynamics have not been demonstrated to correlate with pulmonary function, although DLCO and FVC (forced vital capacity) are pulmonary function tests that can be used to predict the probability of PH. A DLCO < 55% predicted and FVC % predicted / DLCO % predicted > 1.4 was strongly associated with PH in a set of 815 SSc patients.[32]

Finally, Zisman and colleagues also validated a prediction formula for mPAP using standard lung function tests that can be used to screen for PH in IPF patients. This can similarly be applied in CTD-PH-ILD patients, however it has not been validated in this population.

$$\begin{aligned}\text{mPAP} &= -11.9 + 0.272 \times \text{SpO}_2 \\ &\quad + 0.0659 \times (100 - \text{SpO}_2)^2 \\ &\quad + 3.06 \times \left(\frac{\text{percentage of predicted FVC}}{\text{percentage of predicted DLCO}} \right).\end{aligned}$$

DETECT and Australian Scleroderma Interest Group Tools in SSc

Because greater prevalence of PAH is seen in SSc patients, screening guidelines and tools have been validated in SSc. Strategies using composite screening instruments such as the DETECT or Australian Scleroderma Interest Group (ASIG) tools identify patients with SSc-PAH using a composite index. The DETECT algorithm assigns numerical scores to clinical variables and, using a web-based calculator, the score determines need for an echocardiogram and subsequently RHC. The ASIG algorithm uses PFT and NT-proBNP as an indication for RHC. (Table 3)

Table 3. When to Order an Echocardiogram Looking for PH in CTD-ILD

History and exam
• Low oxygenation evidenced by decreased Spo_2 or Pao_2, increasing need for oxygen supplementation
• Rapid desaturation of oxygen with mild exercise or movement
• Worsening dyspnea with stable PFTs and or chest CT
• Preserved lung volumes but worsening exertional dyspnea
• Signs and/or symptoms of right heart failure (edema, JVD, hepatomegaly)
Imaging
• A PA-aorta ratio of >1.0 correlated with mPAP > 20 mm Hg on CT chest
• PA diameter and PA-aorta ratio cutoff values >34 mm and >1.1 on MRI
PFTs and CPET
• Low DLCO and low KCO
• Hyperventilation (low $Paco_2$) to maintain oxygenation (especially during exercise)
• CPET: Low Vo_2-co_2 ratio, Low o_2 pulse
• Ratio of FVC % to DLCO % >1.8 (based on DETECT)
• FVC <55% and ratio of FVC to DLCO (% predicted) >1.4
• Heart rate recovery after 6MWT of >13 b/min
• Declining DLCO without evidence of visually worsening fibrosis (absolute DLCO or change)
Labs
• Elevated NT-proBNP/BNP

Abbreviations: 6MWT, 6-minute walk test; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; co_2, carbon dioxide; CT, computed tomography; CTD-ILD, connective tissue disease associated with interstitial lung disease; DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; JVD, jugular venous distension; KCO, transfer coefficient of the lung for carbon monoxide; MRI, magnetic resonance imaging; NT-proBNP, N-terminal (NT)-pro hormone BNP; PA, pulmonary artery; PFT, pulmonary function test; PH, pulmonary hypertension.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing can also help distinguish the limiting physiology in patients with group 1 and group 3 PH. A ventilatory limitation is a typical feature in patients with ILD but can also occur in PAH. Often, patients with PAH will have resting and peak exercise hypocapnia with low $Petco_2$ versus those with ILD have a more ventilatory limitation. The $P(a\text{-}et)co_2$ gradient, which is the difference between the partial pressure of carbon dioxide on an arterial blood gas ($Paco_2$) minus the end tidal co_2 on capnography, fails to decline or rather, increases in patients with PAH that are exercising.[34]

In patients with severe ILD with severe PH (mPAP ≥ 40 mm Hg), there is a lower Vo_2 peak, higher Ve/Vco_2 slope, and lower peak exercise $Petco_2$ compared to ILD patients without PH.[35]

Imaging

High Resolution Computerized Tomography Findings in PH-ILD: The Goh criteria identifies mild ILD in CTD as <20% involvement on high resolution computerized tomography and <5 % of emphysema. Patients with FVC > 70% are classified as indeterminate despite extent of ILD. Finally, in patients with combined fibrosis and emphysema, a DLCO <40% leads to severe group 3 PH even if fibrosis is modest (10% to 20% on high resolution computerized tomography). In SSc patients, emphysema can occur regardless of smoking status.[3]

Based on the results of the Framingham study, a PA ≥ 29 mm in males and ≥ 27 mm in females is considered to represent abnormal dilation.[36] This is not as sensitive in patients with ILD or CTD that have other reasons for dilated pulmonary arteries. A ratio of PA to aorta of >1.0 correlated with mPAP > 20 mm Hg, with a specificity of 92% and positive predictive value of 96%.[36] The measurement of the main PA and ascending aorta diameters should be done at the level where the PA bifurcates (when both the right and left PA appear to be of similar size) using electronic calipers.[37]

Magnetic Resonance Imaging: Magnetic resonance imaging is more accurate than a computed tomography chest scan. PA diameter and PA-aorta ratio cutoff values >34 mm and >1.1 yielded specificities of 98% and 100%, with corresponding sensitivities of 65% and 50% and positive predictive values of 98% and 100%. Serial magnetic resonance imaging machines have the advantage of demonstrating longitudinal and circumferential RV strain, PA stiffness, and reduced RV and PA coupling.[38]

Echocardiography: The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of PH recommend screening patients with suspicion for PH using a transthoracic echocardiogram. These guidelines recommend yearly echocardiographic screening for all patients with SSc. These guidelines are specific to SSc and not other CTDs because of higher prevalence and mortality in this population.

In other disorders where PH is suspected, a screening echocardiogram is ordered when clinical and noninvasive testing parameters suggest PH. In patients with PH-ILD however, the tricuspid regurgitation velocity jet may be difficult to visualize and may lead to inaccurate estimations of the RV systolic pressure when compared with diagnostic RHC.[28] It is important for the PH provider to review the echocardiograms and interpret other markers of RV dysfunction within the clinical context.[39] (Table 4 and Table 5)

INVASIVE CLUES SUGGESTING PULMONARY VASCULAR DISEASE IN CTD-ILD

RHC remains the gold standard in diagnosis of PH. Left heart abnormalities and PH-ILD can coexist with vasculopathy in many CTDs, hence it is important to clearly determine the hemodynamic phenotype. Diastolic dysfunction is common in CTD because of cardiac fibrosis seen in SSc, idiopathic inflammatory myositis, and mixed CTD. It is also seen more commonly in older patients who have left heart disease risk factors and have CTD. Therefore, we recommend free fluids before the procedure or withholding diuretics for 48 hours. In patients where pulmonary capillary wedge pressure ≤15 mm Hg,

Table 4. Clinical Criteria Favoring Group 1 versus Group 3 PH[a]

Favoring PAH	Testing	Favoring PH-ILD
Extent of lung involvement		
Mildly impaired: FEV 1 > 60% pred FVC > 70% pred Low DLCO relative to obstruction/restriction	PFT	Moderate to very severely impaired: FEV 1 < 60% pred FVC < 70% pred DLCO corresponds to obstructive/restrictive changes
Hemodynamic phenotype		
Moderate to severe PH	RHC Echo	Mild to moderate PH
Ancillary testing		
Present	Group 1 risk factors: BMPR2 mutation, HIV, drug use, schistosomiasis, etc	Absent
CPET		
Exhausted cardiac reserve Low O_2 pulse Lower mixed venous oxygen saturation No change in $Paco_2$ during exercise Low CO/Vo_2 slope		Exhausted ventilatory reserve Reduced breathing reserve Normal O_2 pulse Mixed venous oxygen higher limit Increase in $Paco_2$ during exercise Normal CO/Vo_2 slope

Abbreviations: CO, cardiac output; CPET, cardiopulmonary exercise testing; DLCO, diffusing capacity of lung for carbon monoxide; FEV, forced expiratory volume; FVC, forced vital capacity; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; pred, predicted; RHC, right heart catheterization.

[a]Adapted from: Nathan et al[6]

we recommend a rapid saline bolus to unmask diastolic dysfunction. It is ideal to obtain a wedge saturation >90% to ensure accuracy.[9] Finally, in patients with significant pulmonary disease and PH, pressure measurements during a RHC can be affected by changes in intrathoracic pressures during a breathing cycle. The 6th World Symposium for PH recommends that clinicians use the average mPAP and pulmonary capillary wedge pressure after several breaths (without a breath hold).[40] Reviewing waveforms is therefore of utmost importance.

Poor survival outcomes in the CTD population are demonstrated especially in the SSc cohort. Studies have shown that SSc patients develop greater RV dysfunction independent of the pulmonary afterload. This was demonstrated by Tedford and colleagues[41] when they used invasive RV pressure-volume relations to show differences in RV contractile function. Despite finding no differences in afterload between SSc-PAH, SSc-PH-ILD, and idiopathic PAH, they saw that with increasing afterload, the RV in SSc-PAH patients had a greater inability to compensate.

Table 5. Echocardiographic Parameters that Increase Suspicion for Pulmonary Hypertension[a]

Peak tricuspid regurgitation velocity (m/s)	Presence of echo 'PH signs'	Echocardiographic probability of pulmonary hypertension	RHC Referral
≤2.8 or not measurable	absent	low	No
≤2.8 or not measurable	present	Intermediate	Consider
2.9-3.4	absent		
2.9-3.4	present	High	Yes
≥3.4	Not required		
Echo 'PH signs'			
Ventricles	**Pulmonary Artery**		**IVC and RA**
RV/LV basal diameter ratio >1.0	RV outflow doppler acceleration time <105 msec and/or mid-systolic notching Early diastolic pulmonary regurgitation velocity >2.2 m/sec		IVC diameter>21 mm with decreased inspiratory collapse <50% with a sniff or <20% with quiet inspiration
Flattening of the interventricular septum (LV eccentricity index >1 during systole/diastole	PA diameter>25 mm		Right atrial area (end-systole)>18 cm^2

Abbreviations: IVC, inferior vena cava; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

[a]Adapted from Galiè et al.[39]

This maladaptive response translates to poorer response to vasodilators in severe SSc-PAH patients and is thought to be the reason why there are less echocardiographic changes in SSc-PAH versus idiopathic PAH despite escalation of therapy.[42] It is important therefore to determine RV dysfunction or risk *earlier* in this group of patients. (Table 6)

Table 6. When to Confirm With a RHC

1. Abnormal right sided morphology or function on echocardiogram (see echo PH signs and tricuspid regurgitation velocity m/s)
2. PH will likely be influenced by RHC results
- Possible transplantation
- Inclusion in clinical trials or registries
3. Needing to unmask left heart dysfunction (those with group 2 risk factors such as metabolic syndrome, structural left heart disease, LBBB on ECG, dilated LA, hypertension, type 2 diabetes)
4. Consideration of compassionate use therapy

Abbreviations: ECG, electrocardiogram; LA, left atrium; PH, pulmonary hypertension; RHC, right heart catheterization.

TREATMENT: WHAT THE EVIDENCE CURRENTLY SUPPORTS

PH-Specific Therapy

There has long been controversy regarding the use of PAH-specific therapy in PH-ILD. Despite progressive strides in treatment options for PAH, a treatment approach to PH-ILD has largely been expert-led rather than evidence-based. The currently accepted treatment approach is to correct or prevent progressive hypoxemia by treating the underlying lung disease with immunosuppression and/or antifibrotics, preventing progression, and considering lung transplantation when not contraindicated.[43]

One of the barriers is the lack of consensus regarding the definition of disproportionate PH in chronic respiratory disease and the danger of causing worsening gas exchange through inhibition of hypoxic pulmonary vasoconstriction. Secondly, most trials enrolled patients using diffusion capacity or transthoracic echocardiogram criteria to diagnose PH rather than through invasive hemodynamics.[23] Finally, the prognosis is so grim that often life expectancy is short, making enrollment challenging. Clinicians are hesitant to enroll patients in a trial that might commit patients to placebo or worsen their already poor prognosis and quality of life.

Unfortunately, the pathogenesis of PH-ILD being multifactorial and the reversal of hypoxia rarely reverses PH in patients.[43]

Despite this, a survey looking at current practice patterns in PH providers reveal that PAH-specific therapies are still prescribed to patients with PH-ILD. Practitioners state that the factor influencing their decision to treat was usually RV dysfunction or RV failure.[44] Clinicians have long been treating what they believed was a predominantly circulatory rather than ventilatory dysfunction.

The data for group 3 PH-ILD is mostly from the idiopathic interstitial pneumonias, particularly IPF, and have shown little benefit[45] until the recent INCREASE study.[46]

And yet with SSc-ILD-PH, PH-specific therapy has demonstrated mixed results. At expert PH centers, patients with SSc-ILD-PH are often given a trial of pulmonary vasodilators with the hope of treating a responsive arteriopathy.[23]

Clinical trial data in CTD-PAH demonstrate that PH-specific therapies such as prostacyclins, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors have been shown to improve exercise tolerance, health-related quality of life, and hemodynamic parameters.[15] Unfortunately, not the same can be said with trials that included populations that had ILD. Patients with ILD have been historically excluded, however, with the exception of a few trials in SSc.

Mathai and colleagues found a 3-year survival rate of 39% among patients with SSc-PH-ILD who were on PH-specific treatment. It is unclear if this was because of worsening disease progression and the known disease course of these patients versus the effects therapy.[25]

Sildenafil: Small observational studies in IPF and oral sildenafil and tadalafil (phosphodiesterase type 5 inhibitors) have demonstrated improved ventilation-perfusion matching with oxygenation.[45] Furthermore, incident patients in the COMPERA registry who were treated with phosphodiesterase type 5 inhibitors demonstrated a median improvement in 6MWD of 24.5 m, and close to a quarter of patients had improved functional class.[47] Importantly, many studies in this population demonstrated no gas exchange abnormalities[45] and rarely resulted in trea tment withdrawal. Reductions in oxygen delivery because of pulmonary vasodilation is thought to be compensated for by an increased cardiac output that may maintain or even improve tissue oxygen delivery most notably during exercise.[6] This is further supported by a post hoc subgroup analysis of the STEP-IF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) trial where RV dysfunction by echocardiography was improved and they found a mean increase of 99.3 m (95% confidence interval, 22.3-176.2 m) in their 6MWD at 12 weeks compared with baseline.[48]

In CTD-PH-ILD patients, a small retrospective observational study of 13 CTD-PH-ILD patients who were treated with bosentan, sildenafil, or bosentan plus sildenafil revealed that despite no change in exercise tolerance, FVC, and 6MWD, treatment was tolerated with no untoward side effects.[49]

In another study of 10 patients with CTD and moderately elevated pulmonary pressures (mPAP ≥ 21 mm Hg), Reith et al found that sildenafil 20 mg 3 times daily for 90 days reduced the median total pulmonary resistance during exercise 6.22 mm Hg/min/L (IQR 4.61, 8.54) to 5.24 mm Hg/min/L (IQR 3.95, 6.96) ($P = .005$) and increased median pulmonary arterial capacitance during exercise 1.59 mL/mm Hg (IQR 0.93, 2.28) to 1.74 mL/mm Hg (IQR 1.12, 2.69) ($P = .005$).[50] This was independent of their mPAP, suggesting that vasodi-

lator therapy is beneficial in improving the hemodynamics response to exercise in CTD.

Interestingly, a small phase IIB/III trial of fibrotic ILD patients who have yet to develop PH but were on long-term oxygen treated with pulse inhaled nitric oxide demonstrated increased moderate vigorous activity on actigraphy.[51]

BUILD Trials: Despite smaller studies demonstrating efficacy of prostacyclins and endothelin receptor antagonists in SSc-ILD,[52,53] randomized controlled trials on the efficacy of bosentan and macitentan in IPF and SSc-ILD demonstrated no change in 6MWD.

RISE-IIP: The soluble guanylate stimulator riociguat in PH-ILD was used in a pilot trial to evaluate safety in idiopathic interstitial pneumonias (IIP) with RHC-confirmed PH and was terminated early for increased rates of serious adverse events and death in the treatment group both in the randomized trial and the crossover arm of the open-label extension. There was no improvement in 6MWD in patients treated with riociguat.[54]

INCREASE Study (Treprostinil): Treprostinil, a prostacyclin analogue, promotes vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. Data suggests that there is an added antifibrotic property in its ability to affect extracellular matrix remodeling and fibrosis in vivo by decreasing fibrocyte recruitment to sites of vascular remodeling.[55] This is the first trial to successfully address PH-ILD. CTD-ILD comprised 22% of the population. Compared with placebo, treprostinil improved exercise capacity as demonstrated by an increase in 6MWD from baseline at 16 weeks. Secondary endpoints that were met included a decrease in the NT-proBNP by 15% from baseline with inhaled treprostinil and increased 46% from baseline with placebo, decreased risk for clinical worsening, and less exacerbations in the treprostinil group.

Surprisingly, a subgroup analysis showed that in patients with a resistance of ≥5.275 Wood units there were also improvements in FVC at 16 weeks. This trial's success is met with caution, however, as the use of inhaled treprostinil requires thoughtful phenotyping of the PH and an understanding of hemodynamics. While there is excitement to use a medication in a disease that previously had no therapeutic options, we recommend that the decision to initiate inhaled treprostinil be done in conjunction with an expert PH center and that realistic expectations regarding benefit to quality of life should be discussed with patients. (Table 7 and Table 8)

Table 7. When to Consider Initiation of Inhaled Treprostinil (Tyvaso)[a]

PVR ≥ 3 WU, PCWP < 15 mm Hg Relative risk considerations: • Median PVR of patients in INCREASE was 6 WU • Subgroup analysis of participants that saw the most benefit was PVR ≥ 4
≤6 L of supplemental oxygen at rest unless being referred for transplantation Ambulatory distance of >300 feet Not a hospice or nursing home candidate

Abbreviations: PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; WU, Wood units.

[a]Other clinical trials using PH-specific therapy are summarized in Table 8.

ILD-Specific Treatment: Antifibrotics and Immunosuppression

A discussion on the prevention of progressive fibrosis in CTD-ILD requires separate discussion. We emphasize its importance in prevention of progression

Table 8. PH-Specific Therapies in CTD-PH-ILD

Author	N	Drug	Trial	Outcomes	CTD
Mittoo (2010)[15]	13	Bosentan/ sildenafil	Retrospective	No decrease in 6MWD or FVC in 24 months	CTD-ILD
Heresi and Minai (2008)[52]	19	Epoprostenol and bosentan	Retrospective	15/19 had improved 6MWD > 50 m	SSc-ILD
Ahmadi-Simab et al (2006)[53]	8	Bosentan	Open label, prospective	Improved 6MWD and WHO FC	SSc-ILD
BUILD 2 Seibold et al (2010)[56]	163	Bosentan	RCT	No change in 6MWD	SSc
Furuya and Kuwana (2011)[57]	9	Bosentan	Open label	No effect on lung function decline	SSc
RISE-IIP Nathan et al (2019)[54]	147	Riociguat	Double-blind, placebo-controlled RCT	no improvement in 6MWD ↑adverse events	IIP
Baughman et al (2014)[58]	39	Bosentan	Double-blind, placebo-controlled RCT	Change in mPAP	Sarcoidosis
INCREASE Nathan et al (2021)[55]	326	Inhaled treprostinil		Change in 6MWD FVC	IIP (20% had CTD)

Abbreviations: 6MWD, 6-minute walk distance; CTD, connective tissue disease; FC, functional class; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonias; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; RCT, randomized controlled trial; SSc, systemic sclerosis; WHO, World Health Organization.

to the CTD-PH-ILD phenotype in the model we previously discussed. If clinicians managing CTD-ILD are able to halt or slow progression, there may be improvement in this group with the worst prognosis.

More importantly, in vitro data on antifibrotics have not only demonstrated an ability to slow down the initiation and progression of lung fibrosis, including the release of proinflammatory and profibrotic mediators, but also to inhibit the vascular cell proliferation.[59] With the recent approval of antifibrotic medications for fibrosing ILDs such as IPF and SSc-ILD, we may potentially see a decrease in the incidence of PH-ILD and PAH in the future.

Supportive Care: We recommend supplemental oxygen to keep oxygen saturation ≥90%. Supplemental oxygen to treat lung disease is first line in patients with PH-ILD (supplemental oxygen). Additionally, because of the known increased incidence of sleep disordered breathing in PH, we recommend that patients be screened and treated for coexisting sleep apnea. Pulmonary rehab and consideration of early palliative care is key to preventing deterioration and focusing on patient-centered goals and health-related quality of life.

Considering Palliation and Hospice

Despite sound physiologic evidence for benefit, treatment of this high risk group will require a constant evaluation of clinical risk versus benefit. As most patients with CTD also have diastolic dysfunction, patients may demonstrate volume overload, recurrent hospitalizations and worsening symptoms that makes their overall quality of life worse rather than better. We recommend this guide for clinicians deciding to remove pulmonary hypertension specific therapy. The patient clinician relationship requires a clear communication of risk and mutual understanding of clinical benefit for patients to derive the most out of any attempted treatment. (Table 9)

Table 9. When to Stop Inhaled Treprostinil (Tyvaso)

• Not tolerating due to diastolic dysfunction • Volume overload • No added benefit to quality of life • Continuing to decline due to hospice trajectory
Clinical markers of worsening include weight gain >3 lbs, worsening hypoxia

SUMMARY

The development of PH in CTD-ILD is usually a consequence of worsening advanced lung disease, a primary result of vascular inflammation due to the CTD itself or a combination of both. Clinicians must be on the lookout for markers of disease progression such as early desaturation, impaired heart rate recovery, worsening gas exchange despite stable lung volumes, and imaging. The critical point at which the progression is mediated by a vasculopathic driver is when PH-specific therapies may be most useful at improving outcomes. Despite worsening ventilation-perfusion mismatch, augmenting cardiac output may eventually relieve hypoxia in some patients.

A combination of antifibrotic, immunosuppressive and vasodilating agents may be the key to slowing progression toward this devastating disease. The recent success of inhaled prostacyclins in this subgroup[55,60] may be credited to the drug delivery mechanism as well as some inherent antifibrotic properties as well.[27]

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