REGULAR ARTICLE

Pulmonary Hypertension Associated With Parenchymal Lung Disease

Rahila Ogunnaike, MD
Division of Pulmonary & Critical Care Medicine, Cedars-Sinai Medical Center

Yuri Matusov, MD, FACP
Division of Pulmonary & Critical Care Medicine, Cedars-Sinai Medical Center

Pulmonary hypertension (PH) is a frequent occurrence in interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD) and combined pulmonary fibrosis and emphysema and can be associated with higher morbidity and mortality than pulmonary arterial hypertension. Historically, PH therapy has not been shown to improve outcomes in patients who have PH associated with parenchymal lung disease until more recent approval of inhaled treprostinil in PH-ILD. Unfortunately, this success has not been replicated in PH-COPD. More careful selection of patients who have a predominantly pulmonary vascular phenotype in treatment with PH therapy may be beneficial, and novel trial design may be helpful to determine subgroups within this blanket category who may benefit. Finally, it is critical to approach patients with PH and parenchymal lung disease in a comprehensive fashion, addressing all aspects of medical, psychological, and socioeconomic challenges faced by patients and their caregivers.

INTRODUCTION

Pulmonary hypertension (PH) is a frequent occurrence in interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), and combined pulmonary fibrosis and emphysema (CPFE). Although precise estimates are difficult, among patients undergoing lung transplant evaluation for idiopathic pulmonary fibrosis, approximately 46% of patients are found to have PH, and the incidence ranges from around 10% to 15% in patients with ILD associated with systemic sclerosis and 20%–25% in patients with ILD associated with mixed connective tissue disease (CTD).[1–3] In patients with COPD, the prevalence of PH is around 30%–40%, with around 5%–7% of patients experiencing severe disease.[4,5] Furthermore, patients with CPFE likely have a higher incidence and more severe pulmonary vascular disease than those who have emphysema or pulmonary fibrosis alone.[6]

Patients with coexisting lung disease and PH have a prognosis which is markedly worse than that of patients with pulmonary arterial hypertension (PAH). As an example, in 1 registry, patients with World Symposium on Pulmonary Hypertension Group 3 PH had a 5-year survival of under 40%, while patients with PAH had an overall 5-year survival of just over 60%.[7] Significant differences in survival have been found between patients who have PH associated with emphysema, CPFE, non-IPF ILD, and IPF.[7] The combination of these conditions significantly impacts patients' quality of life, frequency and duration of hospitalizations, and health care costs.[8]

DIAGNOSTIC CHALLENGES IN PH ASSOCIATED WITH CHRONIC LUNG DISEASE

Apart from systemic sclerosis,[2] no well validated screening algorithms exist for PH in patients with ILD, COPD, or CPFE. Patients who have CTD or other ILD are often evaluated for PH when they have low diffusing capacity, particularly out of proportion to extent of restrictive lung disease, when they have an elevated pulmonary artery (PA) size or PA : aorta ratio on computed tomography scanning, when they have serologic positivity known to be strongly associated with PH, or when they have cardiopulmonary symptoms out of proportion to or not consistent with the known manifestations of their CTD or other ILD.[9–11] A similar approach, focused on signs and symptoms out of proportion or inconsistent as well as elevation in B-type natriuretic peptide, is used to trigger echocardiographic screening for PH in patients with COPD and CPFE.[12]

Screening for PH by transthoracic echocardiography is limited in its accuracy of detection and estimation of PA pressure, particularly in patients with parenchymal lung disease.[13] Thus, right heart catheterization (RHC) remains the best tool for diagnosis of PH this population, but patient selection for RHC remains inconsistent outside of populations undergoing transplant workup or clinical trial consideration, and PH in ILD and COPD likely remains underdiagnosed. The RHC hemodynamic thresholds of mean PA pressure >20 mmHg, PA occlusion pressure ≤15 mmHg, and pulmonary vascular resistance (PVR) ≥3 Wood units are identical in World Symposium on Pulmonary Hypertension Group 1 and Group 3 PH, and classification

Correspondence: yuri.matusov@cshs.org
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is dependent on the assessor's attribution of pulmonary vascular disease to parenchymal lung disease or to another underlying cause.[14]

EVOLVING UNDERSTANDING OF PH ASSOCIATED WITH CHRONIC LUNG DISEASE

The traditional understanding of PH development in chronic parenchymal lung disease has rested on the combination of diffuse hypoxic vasoconstriction and architectural distortion of lung parenchyma leading to a rise in PA pressure and PVR. Increasingly, however, the relationship has been recognized between parenchymal changes and pulmonary vasculopathy as significantly more complex (Figure 1). For example, endothelin-1, a known culprit in PAH, is overproduced in IPF and may drive progressive pulmonary fibrosis independently of pulmonary vasculopathy,[15] which was the basis for several trials of endothelin receptor antagonists (ERAs) in ILD, discussed below. Furthermore, genetic predisposition through BMPR2 mutation, inflammation and oxidative stress from underlying lung disease, or from the underlying CTD, when present, may increase patients' predisposition to ILD and PH.[16] Similar pathways of proinflammatory cascade leading to endothelial dysfunction may also contribute to the development of PH associated with COPD.[17] The parallels in the pathogenesis of PH with ILD and COPD are reflected in histopathologic similarity of vascular remodeling between these patients' and that of patients with PAH.[14]

Importantly, it is well established that the severity of ILD does not correlate with development of PH; it has been demonstrated that reduction in forced vital capacity, extent of radiographic fibrosis, and elevation in mean PA pressure are unrelated in IPF and CTD-ILD.[1,18–20] This is important for several reasons. First, it means that clinicians should consider evaluation for PH in all patients with ILD, not just those with advanced disease. Second, it highlights the possibility of predominantly vascular and predominantly parenchymal disease phenotypes, which can suggest the utility of using PAH therapies in patients with ILD.

Guideline and expert opinions on this topic have largely left treatment decisions for patients who have severe PH with significant parenchymal changes up to clinicians and individualize care.[21] Among patients who develop significant pulmonary vascular disease in the context of parenchymal lung disease, symptom burden and mortality are largely driven by consequences of PH, such as right heart failure; this raises the question of whether screening for PH and treating earlier, rather than waiting for disease progression, can improve patient outcomes.

CLINICAL TRIALS IN PH ASSOCIATED WITH ILD

Multiple negative randomized controlled trials (RCTs) of ERAs as well as sildenafil alone or combined with antifibrotic therapy in patients with IPF have been done. Authors of these studies generally either excluded or were agnostic to the presence of PH and were designed to be ILD trials. Investigators of 2 of the trials published subset analyses of patients with PH and ILD—a subgroup of patients with mild (mean PA pressure [mPAP] = 30 mmHg, PVR = 3.9 Wood units) Group 3 PH in ARTEMIS-IPF (n = 68)[22] and a subset of patients with right ventricular dysfunction in STEP-IPF (n = 119).[23] No obvious difference was found for outcomes in the ARTEMIS subgroup, and the STEP-IPF subgroup

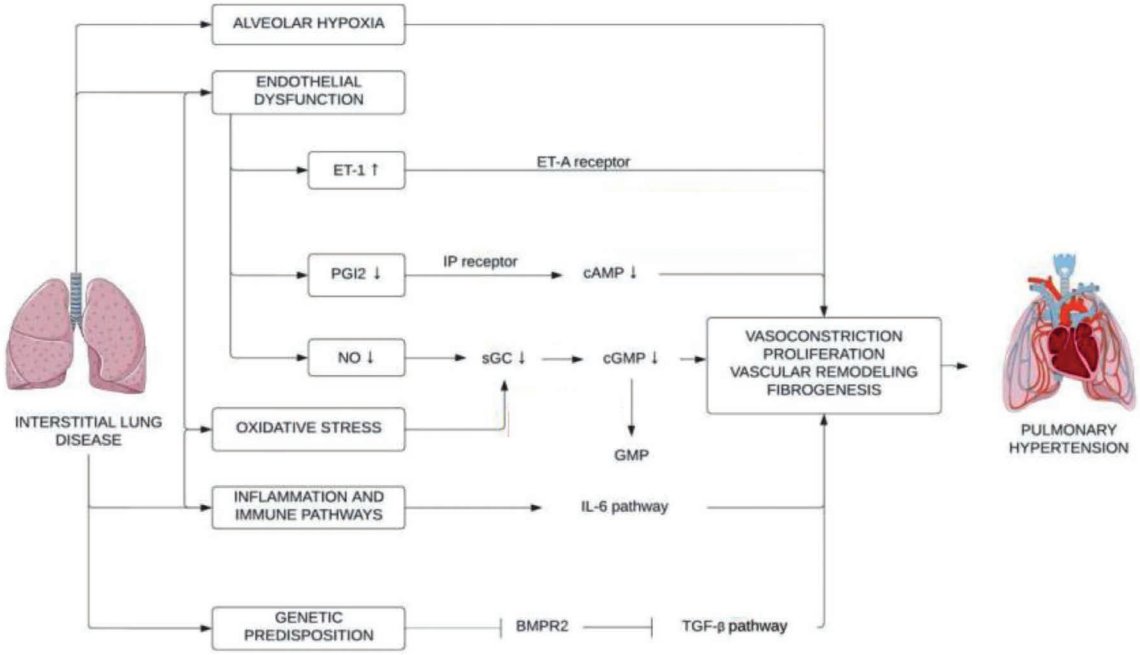

Figure 1: Proposed pathophysiologic mechanisms in the development of pulmonary hypertension (PH) and interstitial lung disease (ILD). Adapted from Dhont et al.[16] Reproduced under Creative Commons Attribution Noncommercial License 4.0.

with RV dysfunction had a lower reduction in 6-minute walk distance (6MWD) and improvement in quality of life on sildenafil.

Authors of several prospective, open-label, registry, and retrospective series have suggested a benefit to treatment of patients with PH-ILD with systemic pulmonary vasodilators, including phosphodiesterase 5 inhibitors, ERAs, and systemic prostacyclins. The benefit seen in these studies seemed to be most prominent among patients with severe PH (mPAP > 35 mmHg), who respond to therapy early and robustly, and those who had CTD-ILD (particularly systemic sclerosis).[24–26] Authors of an early single open-label study[27] of patients with ILD and PH assigned to intravenous (IV) epoprostenol or sildenafil 50 mg suggested a slight increase in V/Q mismatch with aggressive uptitration of IV epoprostenol (no V/Q change with sildenafil), which was not associated with adverse events and has not been reproduced since. None of the authors of subsequent trials of pulmonary vasodilators in ILD without PH, published prospective case series—including 1 of IV treprostinil in severe ILD with PH awaiting lung transplant[28]—or registry or retrospective series suggested worsening hypoxemia with systemic pulmonary vasodilators.

Investigators of 3 RCTs specifically evaluated patients with PH and ILD. In BPHIT (n = 60), no difference was found in PVR index reduction among patients with moderate PH receiving bosentan as compared with placebo.[29] RISE-IIP (n = 229) was stopped early due to safety concerns (in part related to adverse events in patients with CPFE and significant emphysema) in patients receiving riociguat, and investigators found no difference in 6MWD at 26 weeks as compared with placebo.[30]

Most recently, in the INCREASE trial (n = 326), a significant improvement of 31 m was demonstrated with inhaled treprostinil over placebo in patients with ILD (a mix of IPF, CTD-ILD, and others) and PH (mPAP = 37 mmHg, PVR = 6.2 Wood units),[31] even among patients with less severe hemodynamics.[32] A secondary endpoint was lower clinical worsening in the treprostinil arm, and authors of a subsequent post hoc analysis have suggested a reduction in disease progression events and a survival benefit to inhaled treprostinil.[33,34] It should be noted that the benefit was greatest at a dose of ≥9 inhalations 4 times daily. However, enthusiasm has been tempered somewhat by a fairly high discontinuation rate (almost 10% stopped treprostinil due to intolerance in the study, and most experts' real-world experience has suggested much higher discontinuation rates), lack of independent adjudication of clinical worsening events, and the use of a nebulized treprostinil device, rather than the more commonly prescribed dry powder inhaler used today. In fact, in some large-volume centers, patients with PH-ILD are started on nebulized treprostinil, rather than dry powder inhaler, due in part to a lower rate of discontinuation.[35] Nonetheless, inhaled treprostinil represents an exciting potential treatment in a disease with few other options. In the long-term extension study of INCREASE, continued inhaled treprostinil was associated with ongoing improvement in 6MWD and reduced risk of exacerbation as compared with placebo.[36]

Consideration of inhaled treprostinil has a class IIb, level B recommendation for PH-ILD, and phosphodiesterase 5 inhibitors have a Class IIb, level C recommendation for ILD associated with severe PH in the 2022 European Society of Cardiology/European Respiratory Society guidelines.[37] Inhaled treprostinil is the only currently Food and Drug Administration–approved therapy for PH associated with ILD (see Table 1).

CLINICAL TRIALS IN PH ASSOCIATED WITH COPD

Authors of several small RCTs have evaluated systemic pulmonary vasodilators, mainly sildenafil and bosentan, in patients with COPD and PH. These have had mixed results. Authors of 2 trials of sildenafil 20 mg 3 times daily and 1 trial of bosentan in patients with COPD and PH by either echocardiogram (PA systolic pressure

Table 1. Randomized Controlled Trials of PH Associated With ILD

Trial	Study population	Intervention	PH diagnosis and characteristics	Primary outcome
ARTEMIS-PH[22]	Subset of ARTEMIS-IPF (14% of cohort)	Ambrisentan	RHC: mPAP 30 mmHg	No obvious difference (underpowered)
STEP-IPF subgroup[23]	Subset of STEP-IPF (66% of cohort)	Sildenafil	Right ventricular systolic dysfunction	Smaller drop in 6MWD on sildenafil; improvement in QoL
BPHIT[29]	IIP + PH	Bosentan	RHC: mPAP 37 mmHg	No difference in PVR index reduction >20% between groups
RISE-IIP[30]	IIP + PH	Riociguat	RHC: mPAP 33 mmHg	No difference in 6MWD; stopped early due to increased harm with riociguat
INCREASE[31]	ILD + PH	Inhaled treprostinil	RHC: mPAP 37 mmHg	31.1 m improvement in 6MWD over placebo

Abbreviations: 6MWD indicates 6-minute walk distance; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; mPAP, mean PA pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; RHC, right heart catheterization.

>40 mmHg) or RHC suggested improvements in 6MWD, quality of life, and PVR[38–40]; however, authors of other trials have had contradicting results.[41,42] Authors of only 1 study[43] of bosentan in COPD associated with PH suggested worsening hypoxemia with no similar signal in any other trial.

Most recently, a larger RCT of inhaled treprostinil in PH associated with COPD (PERFECT) was stopped early after an interim analysis suggested a higher rate of serious adverse events in the treprostinil group.[44] In this trial, investigators attempted to enrich for a pulmonary vascular phenotype (mPAP ~ 44 mmHg and PVR = 7–8 Wood units in all groups) and failed to demonstrate improvement in the primary endpoint of 6MWD, although its early termination meant that the trial was underpowered for this conclusion. Although it is not entirely clear what contributed to this safety signal, it is possible that the inclusion of a significant number of patients with marked reduction in low diffusing capacity (≤25%), who are already at increased risk of morbidity and mortality, contributed to the number of deaths seen in the study. In PERFECT, CPFE was excluded, and so it was mainly a trial of emphysema-PH; in the INCREASE trial, patients with CPFE had a much less robust response to inhaled treprostinil than patients with PH and IIP and CTD-ILD, which may have been due to the extent of emphysematous parenchymal change.

NONPHARMACOLOGIC TREATMENT CONSIDERATIONS IN PH ASSOCIATED WITH PARENCHYMAL LUNG DISEASE

Patients with PH and parenchymal lung disease benefit from expert, multidisciplinary evaluation. This team should ideally be led by a PH specialist who understands the nuances of pulmonary vascular disease in chronic lung disease and often requires collaboration with other specialists, such as rheumatologists and supportive care medicine specialists, to ensure that all aspects of disease are being treated. Patients should be referred early for lung transplant evaluation since delays in referral can mean that patients are too frail, malnourished, or deconditioned to tolerate lung transplant.[45] Early referral can allow for optimization of nutrition, esophageal reflux (if present), obstructive sleep apnea, atherosclerotic disease, and PH among patients with COPD and ILD.[45] In general, most patients with severe or progressive COPD or ILD with PH and age less than 75 years merit lung transplant evaluation, but it should be noted that, historically, older patients have had worse outcomes than younger patients.[46]

It is important to remember that patients with COPD or ILD and PH have multiple comorbid diseases which can significantly affect their trajectory and quality of life. Patients with progressive pulmonary fibrosis should be treated with antifibrotic therapy early, with more supportive data for nintedanib than pirfenidone in reducing the rate of forced vital capacity decline in patients with non-IPF fibrotic ILD.[47] Patients with ILD responsive to immunosuppression should be treated accordingly, sometimes in combination with antifibrotic therapy. Patients who have COPD should be treated with appropriate guideline-directed inhaler therapy, consideration of chronic azithromycin or roflumilast and, more recently, ensifentrine.[48,49]

Patients with PH and ILD or COPD who have resting or exertional hypoxemia should be treated with supplemental oxygen with a goal SpO2 of ≥90%, although the best data for this are in patients with COPD. Patients with nocturnal hypoxemia should be started on supplemental oxygen.[50] Nocturnal noninvasive positive pressure ventilation is indicated for patients with sleep-disordered breathing, common in patients with ILD and COPD,[51] and patients who have chronic hypercapnia (although, again, this is largely extrapolated from patients with COPD).[50,52]

Pulmonary rehabilitation should be considered for all patients, as it may improve exertional tolerance and reduce frailty in patients with PH and ILD and COPD.[50,53–55] Patients who cannot undergo a formal pulmonary rehabilitation program for logistical or financial reasons should be encouraged to engage in regular exercise, while avoiding exertion to the point of chest pain, syncope, or lightheadedness.[50] Patients should be counseled on low-salt diets, appropriately treated with diuretics, and treated for gastroesophageal reflux disease, as appropriate. Finally, all patients who continue to smoke should be counseled on tobacco cessation and appropriate vaccination[50] against influenza, COVID-19,[56] pneumococcus, and respiratory syncytial virus since infection with these pathogens can contribute to exacerbations of underlying parenchymal lung disease and accordingly accelerate decline in lung function.

Most patients with PH of all types experience significant symptom and treatment burden. Quality of life may be worse in patients with PH associated with parenchymal lung disease than in patients with PAH, despite more favorable hemodynamics.[57] Also, an extraordinary physical and psychological burden exists for patients' caregivers. These translate directly to enormous impacts on day-to-day life, mental health of patients and caregivers, and financial challenges faced by patients and their loved ones.[58] Early referral to palliative or supportive care and support groups should be considered, even among patients who are potential transplant candidates, as well as timely and thoughtful discussions about end of life.[59] Supportive care referrals should not be seen as "giving up hope" or focusing on the end of life, as is commonly felt by PH physicians[60] but, on the contrary, helping patients to live their lives as fully as they can. Unfortunately, even among PH centers of excellence, only 5.8% of patients are referred to palliative care, and 43% of these referrals are made at the last visit prior to death.[61] A summary of overall management in PH associated with ILD and COPD is provided in Figure 2.

FUTURE DIRECTIONS

Future trial designers may need to focus on the extent of severity of parenchymal

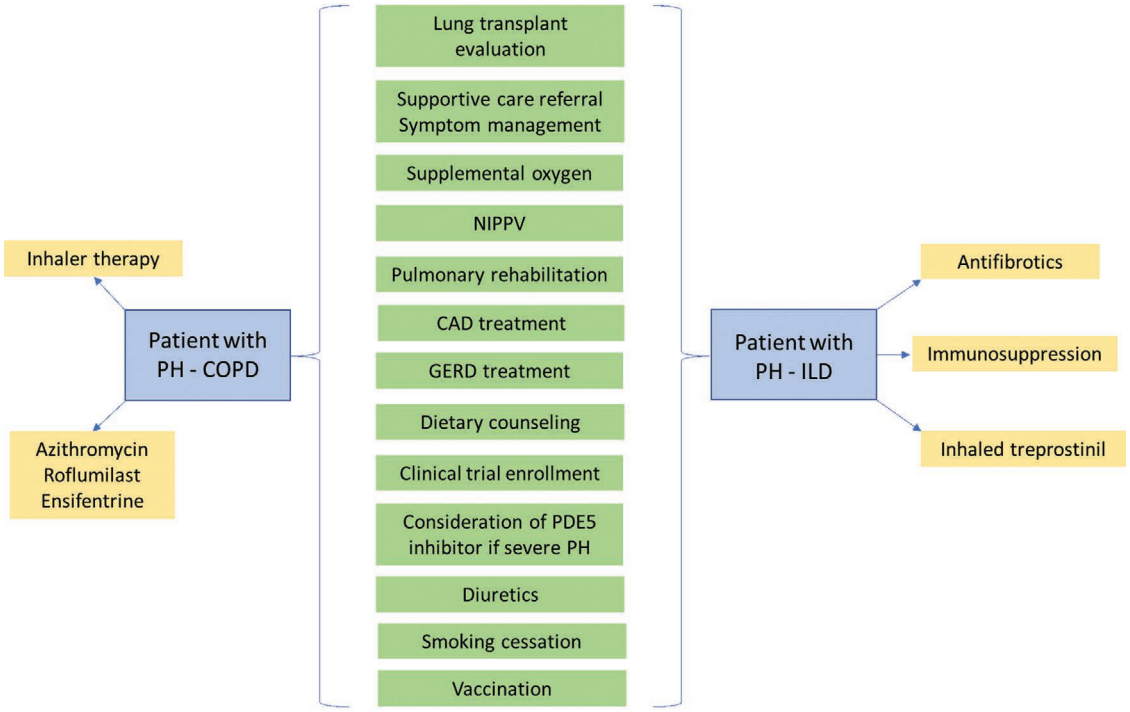

Figure 2: Overall approach to management of patients with pulmonary hypertension (PH) and interstitial lung disease (ILD) or chronic obstructive pulmonary disease (COPD). Abbreviations: NIPPV, noninvasive positive pressure ventilation; CAD, coronary artery disease; GERD, gastroesophageal reflux disease; PDE5, phosphodiesterase 5.

and vascular disease, the specific subtype of parenchymal disease (particularly with differences in patients who have CPFE), and severity of hemodynamics. Furthermore, novel trial design, such as adaptive and event-driven trials and master protocols to optimize efficiency in drug development, may allow for more robust recruitment.[62] Finally, use of trial endpoints past the traditional 6MWD may allow for exploration of more clinically relevant, patient-oriented outcomes.[62]

CONCLUSIONS

Despite recent advances, PH associated with COPD and ILD remains a disease with very high morbidity and mortality and few good treatment options. Although a treatment option now exists for PH-ILD, many patients will be unable to tolerate it, and for many patients, it may not be adequate. Management of these complex patients should be done while keeping in mind the other aspects of their disease. High-quality data are desperately needed in particular phenotypes of patients who suffer from PH associated with COPD or ILD.

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