








# Pulmonary hypertension in the setting of interstitial lung disease: Approach to management and treatment. A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative—Group 3 Pulmonary Hypertension

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## Abstract

Pulmonary hypertension (PH) due to interstitial lung disease (ILD), a commonly encountered complication of fibrotic ILDs, is associated with significant morbidity and mortality. Until recently, the studies of pulmonary vasodilator therapy in PH-ILD have been largely disappointing, with some even demonstrating the potential for harm. This paper is part of a series of Consensus Statements from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative for Group 3 Pulmonary Hypertension, with prior publications covering pathogenesis, prevalence, clinical features, phenotyping, clinical trials, and impact of PH-ILD. It offers a comprehensive review of and a holistic approach to treatment of PH-ILD, including the management of underlying interstitial lung diseases, importance of treating the comorbidities, emphasis on importance of exercise and palliation of dyspnea, and review of the most up-to-date guidelines for referral for potential lung transplant work up. It also summarizes the prior, ongoing, and possibly future studies in treatment of the vascular derangement of this morbid condition.

## KEYWORDS

idiopathic pulmonary fibrosis, management, parenchymal lung disease, pulmonary vascular disease

**Abbreviations:** 6MWD, 6-min walk distance; 6MWT, 6-min walk test; BNP, brain natriuretic peptide; CO, cardiac output; DL<sub>CO</sub>, diffusion capacity for carbon monoxide; ERA, endothelin receptor antagonist; FC, functional class; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; iNO, inhaled nitric oxide; IPF, Idiopathic pulmonary fibrosis; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QOL, quality of life; RCT, randomized controlled trial; RHC, right heart catheterization; V/Q, ventilation/perfusion.

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## INTRODUCTION

Pulmonary hypertension (PH) due to interstitial lung disease (PH-ILD) is a commonly encountered clinical problem with an estimated prevalence of 10%–80% in patients with idiopathic pulmonary fibrosis (IPF) and is also common in other fibrotic ILDs.<sup>1,2</sup> Multiple studies have established that the development of PH is associated with substantial morbidity and reduced survival.<sup>1–3</sup> Until recently, the studies of pulmonary vasodilator therapy in PH-ILD have been largely disappointing, with some even demonstrating the potential for harm.<sup>3–6</sup> This paper is part of a series of Consensus Statements from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative (IDDI) for Group 3 Pulmonary Hypertension, with prior publications covering pathogenesis, prevalence, clinical features, phenotyping, clinical trials, and impact of PH-ILD. The IDDI is a transformational task force within the PVRI that facilitates the development of novel treatments for patients with PH and right ventricular failure. This is done by providing a worldwide platform that encourages an open discussion between academia, regulatory bodies, patient representatives, and pharmaceutical and device companies, thus driving innovative clinical and regulatory therapeutic development strategies. The present manuscript is a focused review providing an overview and update pertaining to the management of PH in the setting of ILD.

## PATIENT PHENOTYPING

A principal diagnostic challenge in patients with a potential diagnosis of PH is to determine, based on a compendium of information including the history, physical signs, pulmonary function tests, imaging, and additional laboratory data, the most appropriate World Symposium Pulmonary Hypertension (WSPH) pulmonary vascular phenotype for an individual patient. This has obvious therapeutic implications since most (but not all) of the available agents are approved for Group 1 and/or Group 4 PH as primarily vascular driven diseases. An example of this frequent dilemma is in connective tissue disease (CTD)-associated PH (particularly scleroderma) where patients with PH could fit into any of the first four groups. For example, Group 1 pulmonary arterial hypertension (PAH) if the lung parenchymal fibrosis is absent or very mild (as is often the case in limited scleroderma), Group 2 disease (with left ventricular dysfunction given the relatively older age of these patients), Group 3 (with more extensive parenchymal fibrosis, particularly in patients with diffuse

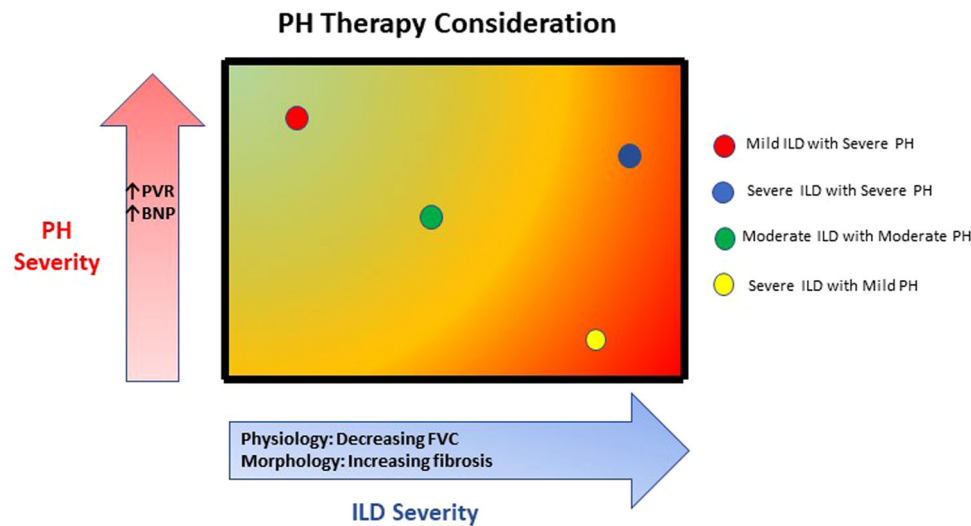
scleroderma), and rarely in Group 4 (chronic clots) or Group 5 (e.g., renal failure) PH. Therefore, a careful integration and interpretation of all clinical and laboratory data is mandatory to determine what is the “best fit” group for an individual patient.

It is increasingly evident that patients may fit into more than one WSPH Group given the presence of associated comorbidities, as noted in several large registries and more recently by the PVDOMICS study group.<sup>7</sup> Distinguishing Group 1 from Group 3 PH is particularly challenging when lung function is preserved, and chest imaging shows mild parenchyma process (Figure 1), with many cases falling within a “grey zone.”<sup>5</sup> As part of this spectrum, a recently coined entity is iPAH with a “lung phenotype.”<sup>8</sup> These patients are typically elderly males with a heavy smoking history and may have occult parenchymal disease such as emphysema without airflow limitation or early stage ILD. In all cases, careful review of the HRCT and integration of all the clinical and laboratory data can help distinguish between Groups 1 and 3 PH (Figure 1).

A frequent lung function threshold employed in various clinical trials and suggested by the WSPH for Group 1 is a forced vital capacity (FVC) > 70% or an FVC between 60% and 70%, provided there are either no or limited parenchymal abnormalities on HRCT.<sup>1,9,10</sup> However, this recommendation is complicated by the fact that lung volume abnormalities correlate poorly with the extent of fibrosis, and that subtle fibrotic changes on HRCT can be associated with significant physiologic derangement.<sup>11,12</sup> A parameter that plays a significant role in the effort at unifying impact of the vascular disease among disparate diseases is the single breath diffusing capacity for carbon monoxide (DL<sub>CO</sub>). A low DL<sub>CO</sub> has been shown to be predictive of high mortality, both in iPAH and PH-ILD.<sup>13–15</sup> A relative disconnect between the severity of PH and the extent of disease on lung function tests or fibrotic findings on HRCT might suggest a primary pulmonary vascular disease process and possibly Group 1 PAH phenotype of the disease.<sup>1</sup>

## TREATMENT OF UNDERLYING ILD

It makes intuitive sense that treating the underlying primary disease should have an impact on the trajectory of associated PH although this concept has not been studied in great depth. Immunosuppressive medications were a mainstay therapy for many forms of fibrotic ILDs, including IPF, until the PANTHER-IPF study demonstrated that this approach was associated with worse outcomes including increased hospitalizations and



**FIGURE 1** Pulmonary hypertension (PH) in interstitial lung disease (ILD) treatment according to disease phenotype. Patients with ILD and PH might present different phenotypes according to the severity of both ILD and PH. These phenotypes sit across a spectrum for both conditions; the phenotype should be taken into account when therapeutic strategies are considered for PH-ILD patients.

mortality.<sup>16</sup> Thus, the use of immunosuppressive medications is not currently recommended in IPF and other fibrotic ILDs.<sup>16–18</sup> Immunosuppressive therapy is still recommended for patients with other forms of ILD when an inflammatory component is thought to be playing a role, such as some connective tissue-related ILD, cellular or mixed nonspecific interstitial pneumonia and, in some instances, chronic hypersensitivity pneumonitis.

Previously, there were no approved therapies to halt or delay the progression of fibrotic lung diseases. However, in 2014 the US Food and Drug Administration approved two drugs, pirfenidone and nintedanib, for the treatment of IPF, ushering in a new era for the treatment of IPF. Subsequently, the 2015 updated ATS/ERS/JRS/ALAT treatment guidelines on the management of IPF included a conditional recommendation for the use of both pirfenidone and nintedanib.<sup>17</sup> Both agents are now variably available in many countries throughout the world. Subsequently, nintedanib was approved for both non-IPF progressive fibrotic lung diseases and scleroderma-related ILD.<sup>18–20</sup> The 2022 ATS Statement on IPF and Progressive Pulmonary Fibrosis (PPF) recommended antifibrotic therapy with nintedanib as a first-line treatment for PPF, thus further cementing the role of antifibrotics in the management of fibrotic ILDs.<sup>18</sup>

The direct effect of either of the antifibrotics on progression of PH has not been studied but warrants further investigation. It is a reasonable hypothesis that by halting disease progression and limiting parenchymal destruction, these medications may have an indirect effect on the development or progression of PH. Conversely, a somewhat fortuitous finding from two

clinical trials of pulmonary vasodilatory drugs is that these agents may have a salutary effect on the progression of fibrosis. In the INSTAGE trial, patients treated with sildenafil and nintedanib had significantly less risk in meeting the composite endpoint of a 5% reduction in FVC or death.<sup>21</sup> In the INCREASE trial, the use of inhaled treprostinil was associated with a significant placebo-corrected improvement in FVC over 16 weeks in the post-hoc analysis of the data.<sup>22,23</sup> In addition, open label long term data showed sustained improvements in FVC over 52 weeks.<sup>24</sup> These results are hypothesis generating and FVC improvement associated with inhaled treprostinil is being prospectively evaluated in patients with IPF, agnostic to the presence or absence of PH, in the TETON studies.<sup>25</sup>

Pirfenidone is a synthetic compound that probably has multiple different mechanisms of action that are still not fully understood; however, the drug appears to have antifibrotic properties via regulation of profibrotic growth factors such as transforming growth factor (TGF)- $\beta$  and tumor necrosis factor (TNF)- $\alpha$ .<sup>26</sup> The conditional recommendation for the use of pirfenidone was based on three large randomized, double-blinded, placebo-controlled trials: the two CAPACITY studies and the ASCEND study.<sup>27,28</sup> Both CAPACITY trials were almost identical phase III, randomized, double-blind, placebo-controlled with change in the percentage predicted FVC from baseline to Week 72 as the primary endpoint.<sup>27</sup> Although the primary endpoint was met in only one of the studies, the two studies together did show a significant difference favoring pirfenidone which was sufficient for the European Medicines Agency to approve

pirfenidone in 2011. However, the combined data set was not met with approval in the United States, and a third study was undertaken. The ASCEND study, the 3rd phase III trial, was a 52-week study and was a positive trial based on the same primary endpoint. This subsequently enabled the approval of pirfenidone in the United States in 2014.<sup>28</sup>

Neither the CAPACITY nor ASCEND trials were individually powered to show a difference in mortality, but combined data from these trials showed a beneficial effect in long-term (up to 120 weeks) all-cause, IPF-related, and on-treatment mortality.<sup>29</sup> Additionally, a post-hoc analysis showed that patients who manifest progression of disease, as defined by either a 10% reduction in FVC, a 15% decrease in 6-min walk distance (6MWD) or hospitalization, continue to derive significant benefit from ongoing therapy with pirfenidone.<sup>30</sup> A meta-analysis also demonstrated that pirfenidone decreased disease progression and mortality in IPF.<sup>31</sup>

Nintedanib is a triple tyrosine kinase inhibitor targeting fibroblast growth factor receptor in addition to platelet-derived growth factor receptor and vascular endothelial growth factor (VEGF) receptor.<sup>32</sup> The Phase 2 TOMORROW trial found that nintedanib favorably impacted the decline in pulmonary function and time to acute exacerbation in patients with IPF.<sup>33</sup> The two replicate Phase III INPULSIS studies both demonstrated a positive effect of nintedanib on the primary endpoint of a reduction in the annual rate of decline in FVC.<sup>34</sup> Additionally, in INPULSIS-2, a significant increase in the time to the first acute exacerbation was observed in the nintedanib arm. Neither the TOMORROW, nor the INPULSIS trials were powered to show a difference in mortality, but a meta-analysis of these three trials demonstrated hazard ratios in favor of nintedanib for both all-cause and on-treatment mortality.<sup>35</sup> A subsequent subgroup analysis of pooled data from the two INPULSIS trials support the beneficial effect of nintedanib in IPF patients with well-preserved lung function.<sup>36</sup> Also, the INPULSIS-ON open-label extension trial showed that IPF patients with severe physiologic impairment (FVC < 50% predicted) derived the same beneficial effects on FVC decline as those patients with less severe disease.<sup>37</sup>

Patients with combined pulmonary fibrosis emphysema syndrome (CPFE) with significant emphysema (greater than the volume of fibrosis on HRCT) and/or significant airflow obstruction were excluded from the studies of both pirfenidone and nintedanib.<sup>27,28,35</sup> A subgroup analysis of the IPF INPULSIS trials with nintedanib found that the presence of mild-to-moderate emphysema did not have any impact on the magnitude of

the antifibrotic treatment effect.<sup>38</sup> According to the most recent Official ATS/ERS/JRS/ALAT Research Statement published in 2022,<sup>39</sup> antifibrotic medications may have benefit in patients with CPFE with IPF and in other forms of pulmonary fibrosis. In addition, inhaled bronchodilators may have benefit in select patients with significant airflow limitation.<sup>39</sup>

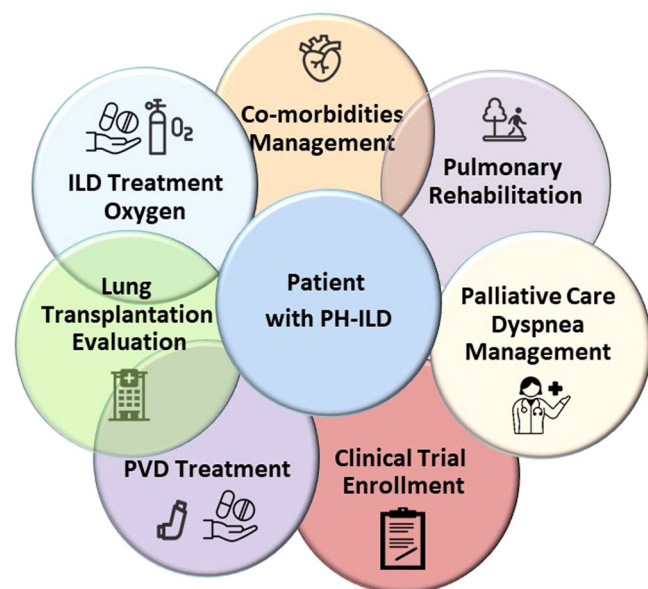
## COMORBIDITIES COMMONLY ASSOCIATED WITH PH IN THE SETTING OF ILD

There are a number of comorbidities that can cause or contribute to the development of PH in ILD. Once PH has been diagnosed, it is incumbent to identify any comorbidity, potentially causative or contributory, since therapies directed at these may impact symptomatology and result in improved quality of life (QOL). Entities to consider include emphysema, sleep disordered breathing and/or obstructive sleep apnea (OSA), heart failure with preserved ejection fraction (HFpEF), coronary artery disease (CAD), cardiac arrhythmias, and acute or chronic thromboembolic disease.<sup>40–51</sup> Diuretics should be used aggressively to treat any fluid overload due to right-sided heart failure. Finally, patients should be referred for pulmonary rehabilitation to address any deconditioning (Figure 2).

Concomitant emphysema has been described in ~28% of IPF patients. A syndrome of ILD and concomitant emphysema is coined CPFE and is often associated with severe PH, which in turn portends a poor prognosis.<sup>41,42</sup>

Hypoxemia should be actively sought and treated. Relying on information from the resting pulse oximetry is not sufficient, as it might not reflect the extent of nocturnal desaturation, or level of desaturation endured during patients' activities of daily living.<sup>43–45</sup> It is also important to be aware that pulse oximetry may underestimate the degree of desaturation and supplemental oxygen needs in patients with dark skin.<sup>46</sup> The 6-min walk test (6MWT) and nocturnal oximetry are important to detect exertional and nocturnal desaturation, respectively. Patients with IPF have a higher prevalence of sleep disordered breathing, and further evaluation with overnight polysomnography should be considered in patients with nocturnal desaturation.<sup>43–45,47</sup>

The role of anticoagulation is unclear as there are no studies evaluating this therapy in PH-ILD. However, patients with idiopathic interstitial pneumonias (IIPs), including IPF, are at increased risk of pulmonary emboli possibly due to decreased mobility and/or a thrombotic predisposition which has been described in IPF.<sup>40,48</sup> An earlier study of anticoagulation in IPF without



**FIGURE 2** Holistic management of PH in ILD. When treating patients with ILD associated with PH it is recommended to take an holistic approach: in addition to considering pulmonary vasodilator drugs, several interventions such as lung transplant referral, optimal oxygen and antifibrotic therapy, the correct treatment for comorbidities, dyspnea and palliative care management, pulmonary rehabilitation and finally enrollment in available clinical trials may help improve the outcomes of these patients. ILD, interstitial lung disease; PDE5-i, phosphodiesterase-5 inhibitors; PH, pulmonary hypertension; PVD, pulmonary vascular disease.

concomitant PH showed a potential mortality benefit of anticoagulation in IPF.<sup>49</sup> The follow-up NIH IPF Network ACE-IPF trial, however, failed to show any benefit for warfarin in the treatment of patients with progressive IPF. Moreover, treatment with warfarin was associated with an increased risk of mortality in IPF patients who lacked other indications for anticoagulation.<sup>50</sup> Nonetheless, if there are other reasons for anticoagulation, such as atrial fibrillation, this should not be withheld. In addition, an analysis of the Pulmonary Fibrosis Registry database did show that the use of direct oral anticoagulants is not associated with increased mortality.<sup>51</sup>

The prevalence of CAD is high (60%) in the IIPs, specifically in IPF.<sup>52</sup> The risk of CAD appears to be independent of smoking, is frequently unrecognized and is associated with worse survival.<sup>53</sup> HFpEF has been described in between 15% and 28% of patients with IPF.<sup>54</sup> In addition, approximately 20% of patients with PH have a postcapillary phenotype due to underlying diastolic heart failure.<sup>55,56</sup> Therefore, a thorough evaluation for both coronary disease and HFpEF should be pursued. With regard to the latter, right heart catheterization (RHC) with fluid challenge can help determine the

contribution of diastolic dysfunction to mechanism of PH and exercise limitation.<sup>57</sup>

In addition to medical treatment of the underlying fibrotic lung disease, comorbidities, and associated PH, referral to palliative care should be considered throughout the course of disease. The morbidity associated with ILD alone is considerable and is made worse by the development of PH. Due to misconceptions that palliative care equates to end-of-life care, referral to palliative care is infrequent in patients with ILD as it is in those with PAH.<sup>58–62</sup> Palliative care should be considered as an integral part of a holistic approach to help patients (and their caregivers) live as well as possible with their conditions and therefore can be considered at any time in the disease course (Figure 2).

## OVERVIEW OF PREVIOUSLY PUBLISHED TRIALS

To date, most clinical trials targeting ILD with pulmonary vasodilators have focused on ILD without PH (Table 1). Although subgroup analyses of patients with PH enrolled in ILD studies have revealed a few promising signals for efficacy, most studies have been negative with a few showing harm.<sup>1,3</sup> To date, in the United States, inhaled treprostinil is the only therapy approved by a regulatory body with an indication for PH-ILD (Tyvaso U.S. package insert).<sup>22</sup>

A number of randomized, placebo-controlled studies have evaluated endothelin receptor antagonists (ERAs) in patients with ILD. There is a rationale for the use of these agents over and above their role as vasodilators. Specifically, preclinical information indicated that endothelin-1 (ET-1) is both profibrotic and a mitogen.<sup>85</sup> ERAs were an obvious choice as treatments of PH-ILD, to tackle both components.<sup>86</sup> In the BUILD-1 study of IPF, bosentan did not significantly improve 6MWD over placebo.<sup>67</sup> In the BPHIT study of patients with fibrotic IIPs and associated PH, treatment with bosentan was not associated with improved hemodynamics, functional capacity, or PH symptoms.<sup>87</sup> The BUILD-3 study failed to show an effect of bosentan on time to clinical worsening or death in patients with IPF.<sup>68</sup>

In the ARTEMIS-IPF study, treatment with ambrisentan was associated with an increased risk for disease progression and respiratory hospitalization resulting in the study being terminated early.<sup>69</sup> A subgroup analysis of patients with PH confirmed by RHC who enrolled in ARTEMIS-IPF revealed similar results to the overall study population.<sup>69</sup> Based on the former study, the 2022 ESC/ERS Guidelines recommend against the use of ambrisentan in patients with IPF-PH.<sup>88</sup> In the MUSIC

TABLE 1 Clinical trials targeting ILD with pulmonary vasodilators.

Lung disease	Investigator	Year	Study design	Pts	Therapy	Results	Comments
<i>ILD/HIP/IPF trials</i>							
IPF	Collard et al. <sup>63</sup>	2007	Open label	14	Sildenafil (N = 14)	57% improved 6MWT by $\geq 20\%$	Median follow-up of 91 days
IPF	Zisman et al. <sup>64</sup>	2010	RCT	180	Sildenafil (n = 89)	Failed to improve 6MWT by $\geq 20\%$	Improved oxygen saturation and QOL
IPF	Jackson et al. <sup>65</sup>	2010	RCT	29	Sildenafil (n = 14)	No difference in 6MWT or Borg score	
IPF	Gunther et al. <sup>66</sup>	2007	Open label	12	Bosentan (n = 12)	No worsening of gas exchange	
IPF	King et al. <sup>67</sup>	2008	RCT	158	Bosentan (n = 74)	Failed to improve 6MWT	Trend to delayed death or disease progression
IPF	King et al. <sup>68</sup>	2011	RCT	610	Bosentan (n = 407)	No effect on time to IPF worsening or death	
IPF	Raghu et al. <sup>69</sup>	2013	RCT	492	Ambrisentan (n = 330)	Terminated early for lack of efficacy in time to clinical worsening	In 32 patients with PH—no change in time to disease progression
IPF	Raghu et al. <sup>70</sup>	2013	RCT	178	Macitentan (n = 178)	Failed to alter primary endpoint of change in FVC	
IPF	Kolb et al. <sup>71</sup>	2018	RCT	274	Nintedanib + Sildenafil (n = 137)	Primary endpoint of change in SGRQ was not met	Enriched for PH (DLCO $\leq 35\%$ )
Fibrotic ILD	Nathan et al. <sup>72</sup>	2020	RCT	45	iNO (n = 23)	Improvement in moderate to vigorous activity and overall activity	Enriched for PH (supplemental O <sub>2</sub> )
<i>PH associated with ILD/HIP/IPF trials</i>							
PH-ILD	Faria-Urbina et al. <sup>73</sup>	2018	Retrospective	22	Treprostinil (inhaled) (n = 22)	Improvement in FC Improvement in 6MWD No change in resting O <sub>2</sub> requirements	
PH-PF	Ghofrani et al. <sup>74</sup>	2002	Open label	16	Sildenafil (n = 8) Epoprostenol (n = 8)	Sildenafil improved V/Q matching and oxygenation	Epoprostenol worsened V/Q matching

TABLE 1 (Continued)

Lung disease	Investigator	Year	Study design	Pts	Therapy	Results	Comments
PH-IPF	Krowka et al. <sup>75</sup>	2007	RCT	51	Iloprost (inhaled) ( <i>n</i> = 26)	No difference in 6MWT, NYHA FC, dyspnea score	
PH-ILD	Chapman et al. <sup>76</sup>	2009	Retrospective	5	Sildenafil ( <i>n</i> = 5)	Improved 6MWT	Decreased mPAP 2–12 months after start of treatment
PH-ILD	Corte et al. <sup>77</sup>	2010	Retrospective	15	Sildenafil ( <i>n</i> = 15)	Improved 6MWT and lower BNP	
PH-ILD	Hoepfer et al. <sup>78</sup>	2013	Open label	22	Riociguat ( <i>n</i> = 22)	Improved CO and PVR but not mPAP	Arterial saturation decreased but mixed-venous saturation increased
PH-ILD	Zimmerman et al. <sup>79</sup>	2014	Open-label, observational	10	Sildenafil ( <i>n</i> = 5) Tadalafil ( <i>n</i> = 5)	Increased CO and decreased PVR	No change in 6MWD or BNP
PH-ILD	Corte et al. <sup>80</sup>	2014	RCT	60	Bosentan ( <i>n</i> = 25)	No effect on hemodynamics, symptoms, or functional capacity	
PH-ILD	Saggar et al. <sup>81</sup>	2014	Open label	15	Treprostinil (parenteral) ( <i>n</i> = 15)	Improved hemodynamics without hypoxemia	All had mPAP $\geq$ 35 mmHg
PH-ILD (CPFE & ILD)	Brewis et al. <sup>82</sup>	2015	Retrospective	118	PDE-5i ( <i>n</i> = 31) ERAs ( <i>n</i> = 11) Prostanoids ( <i>n</i> = 1)	Unchanged 6MWT, decreased BNP in ILD patients	
PH-IIP	Nathan et al. <sup>83</sup>	2019	RCT	147	Riociguat ( <i>n</i> = 73)	Terminated early for unfavorable risk/benefit profile	
PH-ILD	Waxman et al. <sup>22</sup>	2021	RCT	326	Treprostinil (inhaled) ( <i>n</i> = 163)	Improved 6MWD, NT-proBNP, clinical worsening, and FVC	
PH-ILD	Dawes et al. <sup>84</sup>	2022	Retrospective	60	PDE-5i ( <i>n</i> = 50) ERAs ( <i>n</i> = 10)	Patients treated with sildenafil had longer survival	No effect on V/Q mismatching

Abbreviations: 6MWT, 6-min walk test; BNP, brain natriuretic peptide; CO, cardiac output; DL<sub>CO</sub>, diffusion capacity for carbon monoxide; ERA, endothelin receptor antagonist; FC, functional class; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; mPAP, mean pulmonary artery pressure; PDE-5i, phosphodiesterase 5 inhibitor; PF, pulmonary fibrosis; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; RHC, right heart catheterization; SGRQ, St. George's Respiratory Quotient; QOL, quality of life; V/Q, Ventilation/Perfusion; WHO, World Health Organization.

trial, macitentan did not demonstrate any improvements in pulmonary function tests or time to disease worsening or death.<sup>70</sup> Combined with the bosentan data, it appears that the ERA class of medications is not useful and may be harmful in patients with PH-ILD.

Clinical trial data for sildenafil is somewhat mixed.<sup>63–65,71,74,76,77,89</sup> The STEP-IPF trial evaluated sildenafil in 180 patients with advanced IPF (defined by a  $DL_{CO} \leq 35\%$  predicted) and did not meet its primary endpoint of a  $\geq 20\%$  improvement in the 6MWD.<sup>64</sup> There were small but statistically significant improvements in arterial oxygenation and  $DL_{CO}$  in the sildenafil treatment arm with no notable safety signals.<sup>64</sup> Subjects with right ventricular dysfunction treated with sildenafil experienced less decrement in 6MWD and greater improvement in the quality-of-life assessments.<sup>89</sup> The same approach for trial enrichment ( $DL_{CO} \leq 35\%$  predicted) was adopted in the INSTAGE trial, which evaluated sildenafil in combination with the antifibrotic nintedanib in patients with IPF.<sup>71</sup> This study failed to meet its primary endpoint of change in QOL as evaluated by the St. George's Respiratory Questionnaire at 12 weeks. One of the secondary endpoints, the prespecified composite endpoint of death and FVC decline of  $\geq 5\%$ , favored combination therapy with sildenafil and nintedanib.<sup>71</sup> A few studies of sildenafil in ILD (including IPF) and fibrotic ILD with associated PH have shown clinical improvements in 6MWD and brain natriuretic peptide (BNP), but these data are limited by their lack of placebo arms and small sample sizes.<sup>63,65,74,76,77</sup> According to the 2022 ESC/ERS Guidelines, phosphodiesterase 5 inhibitors may be considered in patients with PH associated with ILD on an individual basis, especially in those with severe vascular disease.<sup>88</sup>

Riociguat was evaluated in the RISE-IIP phase 3 study which enrolled patients with IIP and PH confirmed by RHC.<sup>83</sup> Treatment with riociguat did not improve 6MWD, the primary endpoint, and the study was terminated early due to increased serious adverse events and mortality in patients receiving riociguat, both in the randomized portion of the study as well as the open-label extension. Therefore, the 2022 ESC/ERS Guidelines recommend against the use of riociguat in patients with IIP-PH.<sup>88</sup> A subsequent post-hoc analysis of chest CT scans from patients with available studies suggested that the group with advanced CPFE, and the presence of more emphysema than fibrosis, potentially drove the negative signal of the study.<sup>90</sup>

Inhaled nitric oxide (iNO) has been investigated as a treatment to augment the endogenous nitric oxide pathway which may be altered in PH-ILD. Phase 2b/3 trial of pulsed iNO in ILD patients on supplemental oxygen at risk of PH demonstrated that treatment with iNO was associated with improvements in moderate to

vigorous physical activity (MVPA) measured by actigraphy when compared with placebo.<sup>72</sup> Furthermore, during the open label extension patients maintained their activity levels including placebo subjects who transitioned from a decline to maintenance in moderate to vigorous activity.<sup>72</sup> At the time of the submission of this manuscript, according to the company press release, Phase 3 REBUILD trial of iNO45 in patients with fibrotic ILD on supplemental oxygen did not meet its primary endpoint of the change in MVPA.<sup>91</sup>

Prostanoids have also been evaluated in PH-ILD patients. Small studies using parenteral prostanoids have been shown to improve functional class (FC), 6MWD, echocardiographic parameters, and hemodynamics.<sup>81,92</sup> One theoretical drawback of systemic vasodilator therapy in ILD is decreased oxygenation due to worsening ventilation/perfusion (V/Q) mismatch, as was observed in one small study of IV epoprostenol and oral sildenafil.<sup>77</sup> Inhaled therapies may circumvent this concern by causing vasodilation in well-ventilated areas of the lung, thus preserving V/Q matching. This hypothesis was first investigated by Olschewski and colleagues comparing the effects of intravenous prostacyclin, systemic calcium channel blockers versus iNO and aerosolized prostacyclin/iloprost in a randomized order in 8 patients with severe PH secondary to lung fibrosis in 1999.<sup>93</sup> Inhalation of prostacyclin/iloprost or NO caused preferential pulmonary vasodilatation with a decrease in mean pulmonary arterial and pulmonary vascular resistance (PVR) without deleterious effects on oxygenation, systemic blood pressure or pulmonary right-to-left shunt flow, as measured by multiple inert gas analysis. In contrast, both intravenous prostacyclin and systemic calcium antagonists were not pulmonary vasculature selective, resulting in a significant drop in arterial pressure. In addition, prostacyclin infusion caused a marked increase in shunt flow. One patient received long-term treatment with inhaled iloprost showing a tendency toward improvement of hemodynamics and 6MWD during 12 months of treatment. This observation was further supported by a retrospective review of 22 patients with severe PH (mean pulmonary artery pressure [mPAP]  $\geq 35$  mmHg or mPAP  $\geq 25$  mmHg with PVR  $> 4$  WU) associated with parenchymal lung disease (36% COPD, 41% ILD and 23% CPFE) treated with inhaled treprostinil which showed significant improvements in FC and 6MWD without adverse effects on peripheral oxygen saturation.<sup>73</sup>

Despite these early promising reports of inhaled prostanoids in severe PH-ILD, it took another two decades to demonstrate efficacy for this condition. The INCREASE trial, a 16-week randomized controlled trial (RCT) of inhaled treprostinil in patients with PH-ILD, met its primary



endpoint of change in 6MWD at Week 16.<sup>22</sup> The study enrolled patients with various etiologies of ILD, including IPF (44.8%), chronic hypersensitivity pneumonitis (5.8%), CPFE (25.2%), and CTDs (22.1%).<sup>22</sup> The study's secondary endpoints including change in NT-proBNP and time to clinical worsening were also met. Inhaled treprostinil was found to be safe and well tolerated in this patient population and demonstrated the known side effects of the drug, including throat irritation, cough, headache, and diarrhea. The positive outcome of INCREASE trial resulted in FDA approval of inhaled treprostinil for PH-ILD in the United States in early 2021. The ESC/ERS 2022 Guidelines state that inhaled treprostinil may be considered in patients with PH-ILD.<sup>88</sup> In the forward-looking section, the Guidelines asked for long-term data for inhaled treprostinil, which since has been published.<sup>24,88</sup> Treatment of PH in ILD is not addressed in the most recent ATS/ERS/JLA/ALAT 2022 IPF Guidelines.<sup>18</sup> Thus, there are currently no guideline recommendations addressing the use of inhaled treprostinil in the United States, which remains the only country where this therapy is available.

Several post-hoc analyses of the INCREASE trial have suggested that treatment with inhaled treprostinil has additional clinical benefits. One analysis demonstrated that patients across all the ILD etiologies who received inhaled treprostinil were less likely to experience multiple disease progression events compared with placebo.<sup>94</sup> The therapeutic benefits of inhaled treprostinil may be dose-related, as patients who reached a dose of over nine breaths per session four times per day had both a lower rate of clinical worsening, and a higher rate of clinical improvement.<sup>95</sup> More recently, long-term data from the INCREASE open-label extension demonstrated stabilization of exercise capacity and a durable improvement in the FVC.<sup>24</sup> It should be noted that proven efficacy and safety of inhaled treprostinil in both PAH or PH-ILD should not be extrapolated to other PH indications or other causes of Group 3 PH, and separate trials are needed.

A meta-analysis published before the INCREASE trial investigated the effect of PAH therapy on 6MWT in two RCT and four single arm studies in patients with PH-ILD.<sup>96</sup> In the single arm studies, there was a significant improvement in 6MWD (46.2 m; 95% CI, 27.9–64.4), whereas in the RCTs the improvement did not reach statistical significance (21.6 m; 95% CI, –17.8 to 61.0).

## INVESTIGATIONAL THERAPEUTIC AND DEVICE-BASED THERAPIES

Whereas an inhaled compound from the prostacyclin pathway have shown efficacy and safety in PH-ILD recently, several inhaled compounds that work on the

cGMP/sGC are being further investigated in various forms of PH. Two independent soluble guanylate cyclase (sGC) modulators delivered via dry powder inhalers designed to selectively target the lung vasculature are being studied clinically in Group 1 PAH and CTEPH<sup>97,98</sup> and may also have a potential for the treatment of PH due to chronic lung disease. However, at this time it is unknown if they will be studied in PH-ILD in the future. Other inhalation antiproliferative products are currently being investigated in Phase 2 and 3 trials for the treatment of Group 1 PAH, including tyrosine kinase inhibitors imatinib and serralutinib.<sup>99–101</sup> It is unknown if these compounds will be studied in patients with PH due to ILD, although such studies are encouraged.

Bardoxolone methyl, an oral once-daily antioxidant inflammation modulator that acts via Nrf2 pathway, was investigated in a Phase 2 LARIAT study for safety and efficacy in patients with PH. As per a company press release, eight patients with IPF-PH were included, and bardoxolone was found to improve exercise capacity with a 6MWD change of 38 m in this small cohort.<sup>102</sup> It is unknown if further studies of bardoxolone in PH-ILD will be pursued.

Hyaluronan (HA) is a large glycosaminoglycan composed of repeating units of glucuronic acid and N-acetyl-glucosamine. Expression of HA was shown to promote an invasive fibroblast phenotype that increases lung fibrosis. In addition, HA overexpression also results in vascular remodeling and the increased presence of inflammatory cells in the lung.<sup>103</sup> Furthermore, the pathological deposition of HA in the alveolar regions and surrounding small arterioles correlates with the presence of PH.<sup>104</sup> Hymecromone (H01), also known as a 4-methylumbelliferone, is a coumarin derivative that inhibits the synthesis of HA. It is currently being studied in a proof-of-concept Phase 2 safety and efficacy study in patients with PH, including a subset of patients with ILD.<sup>105</sup>

Several medical devices are under investigation for the treatment of PH. In general, they are intended for use in Group 1 PAH, but their mechanisms of action may also be beneficial in Group 3 physiology. In one example, early clinical work suggests that a device-based enhancement of compliance in the pulmonary vasculature may improve cardiac output and unload the right ventricle without worsening V/Q mismatch.<sup>106</sup> In the INCREASE trial, inhaled treprostinil/Tyvaso was delivered via an iNEB device.<sup>22</sup> The FDA recently approved a new dry powder formulation of treprostinil/Tyvaso delivered via a hand-held inhalation device for both Group 1 and PH-ILD patients.<sup>107</sup> LIQ861 is another dry powder formulation of treprostinil palmitil tested in patients with Group 1 PAH in the Phase 3 open label INSPIRE trial.<sup>108</sup> It was

recently granted a tentative approval by the FDA but remains commercially unavailable. A small safety study of this inhaled formulation of treprostinil in patients with PH-ILD is currently recruiting.<sup>109</sup>

## LUNG TRANSPLANTATION

Lung transplantation (LTx) is the only treatment for fibrotic ILD that improves QOL and survival. However, the median survival after LTx for patients with IPF is only ~4.5 years, which is shorter than the average survival after LTx in general.<sup>110–113</sup> Additionally, only a small proportion of patients qualify for this intervention because of the high risks associated with advanced age, significant comorbidities, and the complexity of the surgery, coupled with the judicious use of a scarce resource. The current recommendation is to refer patients with fibrotic ILD for LTx work up early in the course of disease, ideally at diagnosis, due to the unpredictable nature of disease progression, the risk of acute exacerbations, and the associated high mortality.<sup>114</sup> Since the presence of even mild PH significantly increases the risk of death in patients with fibrotic ILD, the development of PH is one of the listing criteria for LTx.<sup>111–114</sup> Specific referral and listing guidelines are summarized in Table 2.<sup>114</sup>

Overall, posttransplant survival rates continue to improve for all disease categories, including fibrosing ILDs.<sup>110</sup> Although there have been conflicting single

center reports on the impact of pretransplant PH on posttransplant outcomes in ILD patients, a large UNOS registry analysis showed that there is no deleterious effect on posttransplant survival in patients who receive BLTx.<sup>115,116</sup>

The choice of the type of procedure (bilateral [BLTx] vs. single [SLTx] lung transplant) in patients with ILD needs further study. BLTx clearly provides a long-term survival advantage in IPF, even after adjusting for other variables.<sup>117–119</sup> In a recent retrospective UNOS analysis of 9191 patients with IPF, 10-year survival rates were 55% for BLTx and 32% for SLTx ( $p < 0.001$ ).<sup>119</sup> When stratified by age, BLTx recipients had improved survival at all age cutoffs, except age  $\geq 70$  years. In addition, BLTx recipients had improved survival across all lung allocation scores ( $<45$ ,  $\geq 45$ ,  $\geq 60$ ,  $\geq 75$ ) and all pulmonary artery pressure categories ( $<25$ ,  $\geq 25$ ,  $\geq 30$ ,  $\geq 40$  mmHg).<sup>119</sup> However, any posttransplant survival advantage of BLTx versus SLTx needs to be weighed against a longer wait time for a suitable pair of donor lungs (BLTx) versus one good lung (SLTx), and hence a higher risk of pretransplant mortality.<sup>120,121</sup> Furthermore, for patients with very severe PH-ILD (arbitrarily defined as mPAP  $\geq 45$  mmHg in this study) unrestricted listing for either a BLTx or SLTx versus only BLTx was associated with a 17% improved rate of the composite primary outcome, defined as the number of days between listing and death, removal from the list for clinical deterioration, or need for retransplantation.<sup>119</sup>

Timing of referral	<ul style="list-style-type: none"> <li>• At diagnosis of UIP</li> <li>• Any form of fibrosis with FVC <math>&lt; 80\%</math> or DL<sub>CO</sub> <math>&lt; 40\%</math></li> <li>• Any form of fibrosis with Relative decline in FVC <math>\geq 10\%</math></li> <li>• Relative decline in DL<sub>CO</sub> <math>\geq 15\%</math></li> <li>• Relative decline in FVC <math>\geq 5\%</math> in combination with worsening of respiratory symptoms or radiographic progression</li> <li>• Use of supplemental oxygen</li> </ul>
Timing of listing	<ul style="list-style-type: none"> <li>• Any form of pulmonary fibrosis with one of the following in the past 6 months despite treatment:               <ul style="list-style-type: none"> <li>Absolute decline in FVC <math>&gt; 10\%</math></li> <li>Absolute decline in DL<sub>CO</sub> <math>&gt; 10\%</math></li> <li>Absolute decline in FVC <math>&gt; 5\%</math> with radiographic progression</li> </ul> </li> <li>• Desaturation to <math>&lt; 88\%</math> on 6MWT or <math>&gt; 50</math> m decline in 6 MWT distance in the past 6 months</li> <li>• PH on RHC or two-dimensional echocardiography (in the absence of diastolic dysfunction)</li> <li>• Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.</li> </ul>

Note: 6MWT, 6-min walking test; DL<sub>CO</sub>, diffusion of carbon monoxide; FVC, forced vital capacity; PH, pulmonary hypertension; UIP, usual interstitial pneumonia.

Source: Adopted from Leard et al. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2021; 40(11):1349–1379.<sup>114</sup>

**TABLE 2** Recommendations for referral and work up for lung transplantation in patients with fibrotic lung diseases.

## PH TREATMENT APPROACH

While contemplating treatment of PH-ILD, it is imperative to do due diligence to phenotype a patient to the best of one's ability.<sup>6</sup> While it is beyond the scope of this paper to delve into the distinction between patients who are more of the Group 1 versus Group 3 phenotype, there are certainly some patients, especially those with underlying CTD-ILD, where phenotyping is difficult (Figure 1). Although this distinction is somewhat arbitrary, every effort should be made in characterizing the patient with PFTs, chest CT imaging, ECHO, and RHC to identify patients with a pulmonary vascular phenotype. HFpEF should be considered in patients with significant risk factors as treatment with pulmonary vasodilators may precipitate pulmonary edema. For patients who are better categorized as Group 1 PAH, the "toolbox" of treatment options is much broader with treatment based on risk stratification reflecting the severity of the underlying pulmonary vascular disease.<sup>88</sup>

Concomitant with the treatment of pulmonary vasculopathy, providers should ensure that the underlying fibrotic lung disease is optimally managed, although no evidence exists that antifibrotic therapy will improve PH specifically.<sup>6</sup> Exertional desaturation needs to be reevaluated on a serial basis and supplemental oxygen prescribed when appropriate. Screening for sleep-disordered breathing and nocturnal hypoxemia should be considered and treated if present. If there is evidence of volume overload, then diuretics should be used to optimize fluid balance. Pulmonary rehabilitation, early lung transplant evaluation, and timely referral to palliative care are all important considerations in the holistic care of these patients (Figure 2).

The recent ESC/ERS guidelines state that the treatment approach to the patients with lung disease and PH needs to be individualized and recommend a referral to a PH center.<sup>88</sup> In addition, the use of PAH medications, other than inhaled treprostinil, is not recommended in patients with nonsevere precapillary PH. While those patients with more severe hemodynamic derangements clearly have worse outcomes than those with mild to moderate PH, the latter group still has a poor prognosis.<sup>111,112</sup> The INCREASE study enrolled patients with mPAP  $\geq$  25 mmHg with a PVR  $\geq$  3 wood units. A prespecified subgroup analysis of the subgroup of patients with PVR  $<$  4 wood units did not show a benefit in 6MWD with a major limitation being the small sample size of patients with milder disease ( $n = 52$ ).<sup>22</sup> In addition, this analysis was not subjected to a multivariate analysis, and other benefits aside from the 6MWD were not evaluated. The ESC/ERS guidelines also state that inhaled treprostinil may be considered in patients with PH-ILD, irrespective of severity.<sup>88</sup>

In addition, sildenafil appears to be safe, well tolerated, and has some efficacy data for treatment of these patients and may be considered where inhaled treprostinil is not available.<sup>63,65,71,74,76,77,79,82,84,89</sup> It is unknown if a combination of sildenafil and inhaled treprostinil provides incremental efficacy. However, given safety profile of both drugs in this population, consideration can be given to dual therapy in patients with severe PH on an individual basis with careful and frequent follow-up after an open discussion with the patient. Based on the published data and ESC/ERS guidelines, riociguat and ERAs are not recommended.<sup>88</sup> Enrollment in clinical trials should be offered whenever possible. For those patients who are potential transplant candidates, early referral to a transplant center for further evaluation and work-up is strongly encouraged. Finally, for patients who are not transplant candidates, involvement of palliative care to help manage dyspnea should be strongly considered.

## SUMMARY

Treatment of Group 3 PH, in general, has relied on the principle of optimizing the treatment of the underlying lung disease and contributory factors, such as heart failure, sleep disordered breathing, thromboembolism, and deconditioning. Given the quality of prior reports, as well as the negative or equivocal results from clinical trials, until recently systemic pulmonary vasodilators have not been recommended in the treatment of PH associated with lung disease. The INCREASE study of inhaled treprostinil has renewed interest in the use of inhaled pulmonary vasodilators in patients with PH due to underlying ILD, with hope for more studies to come in the next several years.

## AUTHOR CONTRIBUTIONS

Oksana A. Shlobin, Paul M. Hassoun, Stephen J. Wort, John A. Scandurra, and Eric Shen were involved in the conception and design of the manuscript, conducted the searches and data extraction as well as wrote the first draft of the manuscript. Oksana A. Shlobin, Lucilla Piccari, and Steven D. Nathan contributed to creation of the figures. All authors contributed to edits of the manuscript, analyzed and interpreted the data, revised the manuscript critically for important intellectual content, approved the final manuscript, and agreed to be accountable for its overall content.

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#### CONFLICT OF INTEREST STATEMENT

Dr. Oksana A. Shlobin has consulted for United Therapeutics, Bayer, Altavant, Aerovate, Janssen&Janssen and Merck, and is on the speaker bureau for UT, Bayer, and J&J. Mr. Eric Shen is an employee of United Therapeutics Corporation and owns stocks/shares in the company. Dr. Lucilla Piccari has received research funding from and served as a speaker for Janssen and Ferrer, advised Janssen, Ferrer, and United Therapeutics as well as received support for attending congresses from Janssen, MSD, and Ferrer, all of which not related to this manuscript. Dr. John A. Scandurra is an employee of Aria CV Inc. and owns stocks/shares in the company. Dr. Paul M. Hassoun serves on a scientific advisory board for Merck, an activity unrelated to the current work. Dr. Stephen J. Wort received honoraria from Janssen, MSD, Bayer, and Acceleron for advisory boards, received honoraria from Janssen for educational activity, received unrestricted research grants from Janssen and Bayer, and travel grants, conference registration and accommodation from Actelion and GSK. Dr. Sylvia M. Nikkho is an employee of Bayer AG. Dr. Steven D. Nathan a consultant for United Therapeutics, Bellerophon, Third Pole, Roche, Boehringer-Ingelheim, Merck, and Daewoong.

#### ETHICS STATEMENT

Not applicable.

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