Pulmonary hypertension in interstitial lung disease: an area of unmet clinical need

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PH is an under-recognised entity in patients with ILD and adversely affects clinical outcomes. Newer therapeutic strategies such as intrapulmonary administration of pulmonary vasodilators show encouraging results, making it worthwhile to confirm diagnosis. https://bit.ly/3AOcfZL

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Abstract

Pulmonary hypertension (PH) is present in an important proportion of patients with interstitial lung diseases (ILDs), encompassing a large, heterogeneous group of diffuse parenchymal lung diseases. Development of ILD-related PH is associated with reduced exercise capacity, increased need for supplemental oxygen, decreased quality of life and earlier death. Diagnosis of ILD-related PH is important and requires a high index of suspicion. Noninvasive diagnostic assessment can suggest the presence of PH, although right heart catheterisation remains the gold standard to confirm the diagnosis and to assess its severity. A comprehensive assessment is needed to make sure reversible causes of PH have been ruled out, including thromboembolic events, untreated hypoxaemia and sleep disordered breathing. The results of trials concerning pulmonary vasodilators in this particular patient group have been disappointing and, in some cases, were even associated with an increased risk of harm. Newer strategies such as medications administered through inhalation and combinations with antifibrotic drugs show encouraging results. Moreover, unravelling the role of the vasculature in the pathophysiology of pulmonary fibrosis and ILD-related PH may potentially unlock new therapeutic opportunities.

Introduction

Pulmonary hypertension (PH) has been divided by the World Health Organization into five distinct categories upon similarities in pathophysiology, clinical presentation and therapeutic options. PH in the context of hypoxia and/or lung diseases, mostly interstitial lung disease (ILD), COPD and sleep-disordered breathing (*e.g.* obstructive sleep apnoea syndrome), has been assigned to group 3 [1]. The prevalence of PH has been reported in up to 86% of patients with ILD, but depends on the definition of PH, the underlying type of ILD and the diagnostic assessment to diagnose PH [2, 3]. The diagnosis of PH in patients with underlying ILD is based on right heart catheterisation (RHC): a resting mean pulmonary artery pressure (mPAP) >20 mmHg and a pulmonary vascular resistance ⩾3 Wood Units are mandatory, as recently updated during the 6th World Symposium on Pulmonary Hypertension [1, 4].

ILD-related PH (ILD-PH) is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life and worse prognosis [1, 2, 4, 5]. A prominent consequence of PH is its adverse impact on the right ventricle (RV). According to the law of Laplace (pressure and radius are correlated with afterload), the initial response to pressure overload is RV hypertrophy [6]. Subsequently, the RV dilates and becomes unable to compensate for the increased afterload, leading to right ventricular failure (cor pulmonale), and eventually reduced cardiac output, indicating a very poor prognosis [7].

Lessons for clinicians

- ILD-related PH is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life and worse prognosis.
- The high co-incidence of ILD and PH can be explained by shared pathophysiology.
- Noninvasive diagnostic assessment can suggest the presence of PH, although right heart catheterisation remains the gold standard to confirm the diagnosis and to assess its severity.
- Promising new therapeutic strategies such as administering pulmonary vasodilators *via* the inhaled route (*e.g.* inhaled treprostinil and nitric oxide) could address this area of unmet clinical need.

Points for future research

- There is no uniform, validated screening algorithm for PH in the setting of ILD.
- Large, long-term trials focusing on clinical primary end-points such as patient-reported outcomes, quality of life, hospitalisations and survival are eagerly awaited.
- Further unravelling of the pathogenesis of ILD-PH has the potential to unlock new therapeutic opportunities.

Despite its impact, there is no consensus regarding screening for PH in ILD. Early detection of ILD-PH depends on the clinical suspicion of the treating physician, and confirming the diagnosis is often challenging. Until now, treatment has been merely supportive, including oxygen, diuretics and optimal treatment of the underlying lung disease. However, promising therapies on the horizon in recently published trials could change this area of unmet clinical need. In this review, we focus on ILD-PH, mainly idiopathic pulmonary fibrosis (IPF)-related PH, and its prevalence, pathophysiology, diagnosis and treatment.

Interstitial lung diseases

ILD is an umbrella term for a heterogeneous group of >150 lung diseases with common functional characteristics (restrictive physiology and impaired gas exchange), but with a wide range of causes, pathological and clinical manifestations and imaging characteristics and variable outcomes [8]. Despite the vast heterogeneity of ILD, most frequently the pulmonary alveolar walls are infiltrated by different types of inflammatory cells and demonstrate proliferation of certain cells (*e.g.* fibroblasts and myofibroblasts). Irrespective of the initial inciting triggers, IPF and some other ILDs are characterised by progressive fibrosis of the lung interstitium, sharing a common final pathway leading to irreversible fibrosis and impairment of gas exchange. These pathological and pathophysiological derangements in progressive fibrosing ILDs are associated with a cascade of clinical consequences including exercise intolerance, respiratory failure, increasing oxygen requirements and eventually death [9, 10].

IPF, chronic hypersensitivity pneumonitis, connective tissue disease related ILD, sarcoidosis and pulmonary Langerhans cell histiocytosis are the ILDs most commonly associated with PH [3, 8, 11]. Importantly, sarcoidosis and Langerhans cell histiocytosis related PH are classified in group 5 (PH due to other causes) due to their multifactorial pathophysiology [12]. For example, mechanisms of sarcoidosis-associated PH mainly include hypoxaemia from ILD, vascular disease, mediastinal distortion/compression from lymphadenopathy and extrapulmonary disease manifestations (*e.g.* left ventricular dysfunction) [13].

Most of the data on PH in patients with ILD originate from the literature concerning IPF. In general, PH in patients with ILD is mild to moderate, and rarely severe. In a large trial in patients with IPF, 46% of patients with advanced ILD had mPAP >25 mmHg, but only 9% had mPAP >40 mmHg [7]. Of note, most of the data used in prior studies included the previous definition of PH, with a mPAP cutoff of 25 mmHg. In a separate series of 70 patients with IPF, receiver operating characteristic analysis suggested a mPAP of 17 mmHg as the best discriminator of mortality [14, 15]. The reported prevalence of IPF ranges from 14 to 43 per 100 000 persons and PH is detected in up to 30–50% of this patient group [12]. The incidence of IPF increases with older age, with presentation typically occurring in the sixth and seventh decades [15]. As to the outcome, PH is associated with a three-fold increase in mortality compared with people with pulmonary disease and no PH [16]. However, according to the COMPERA registry, there is no difference in survival between the different types of ILD associated with PH [4, 17].

Pathogenesis of ILD-PH

The high co-incidence of ILD and PH can be explained by shared pathophysiology concerning parenchymal and vascular remodelling, as conceptualised in figure 1. Whereas epithelial injury has been considered the central protagonist in the development of lung fibrosis, with vascular dysfunction as a secondary side-effect, there are emerging data that the vasculature itself plays a pathogenic role in the incitement of lung diseases [18]. Alveolar hypoxia is well known to cause reactive vasoconstriction (the Euler-Liljestrand reflex) and

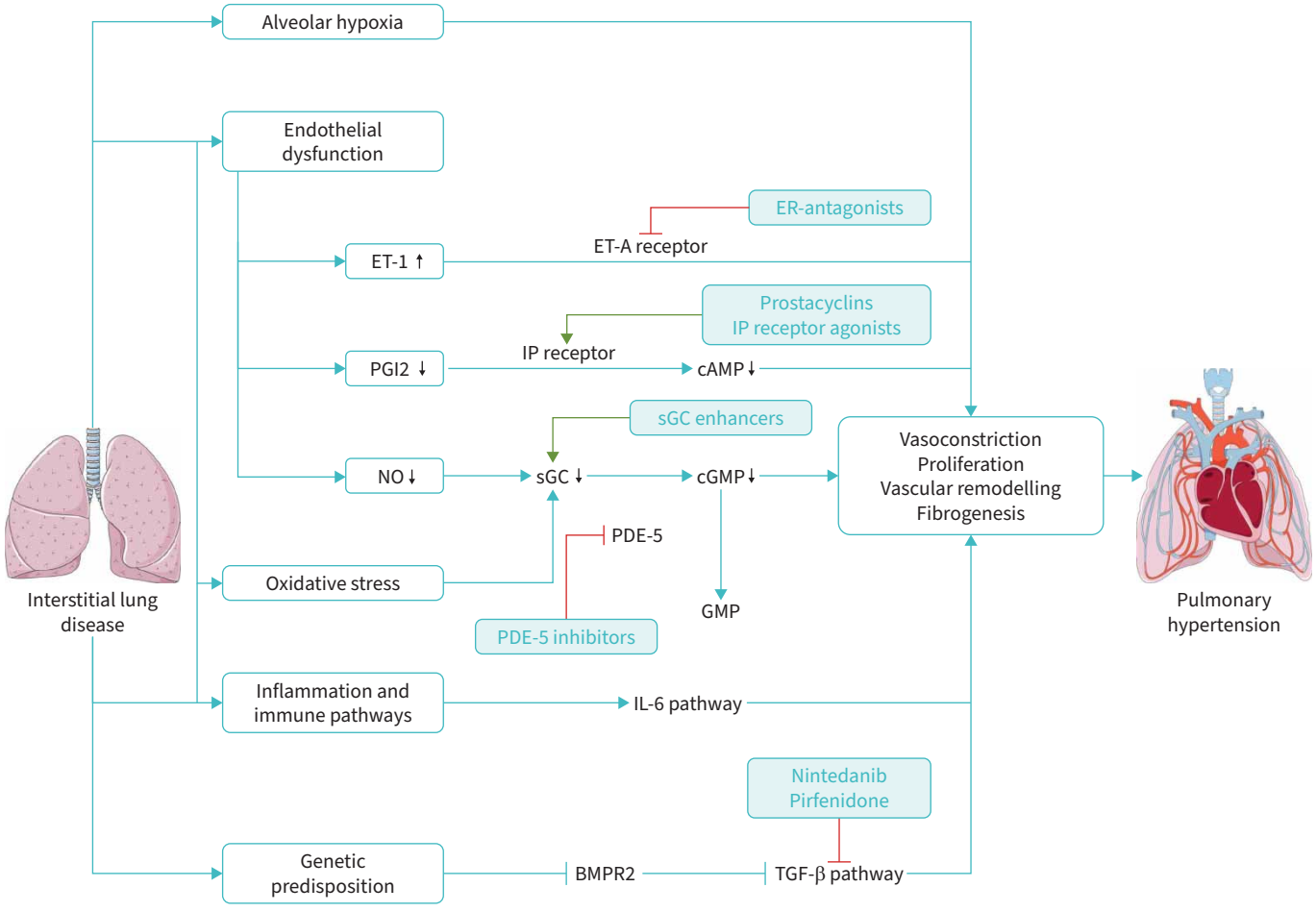

FIGURE 1 The high co-incidence of interstitial lung disease and pulmonary hypertension can be explained by shared pathophysiology concerning parenchymal and vascular remodelling. ET: endothelin; ER: endothelin receptor; PGI2: prostaglandin I2 (prostacyclin); NO: nitric oxide; IP: prostacyclin; sGC: soluble guanylyl cyclase; PDE: phosphodiesterase; IL: interleukin; BMPR: bone morphogenetic protein receptor; TGF: transforming growth factor.

blood redistribution to better-ventilated parts. This phenomenon, in turn, causes increased pressure, wall stress and increased shear forces leading to a cascade of mediators and cellular changes that contribute to vascular remodelling [19]. Nevertheless, PH has been noted to occur in the absence of resting hypoxaemia or advanced pulmonary disease and there is a lack of correlation between mPAP and the degree of abnormalities in pulmonary function testing [3]. Other mechanisms leading to PH in ILD include endothelial dysfunction, oxidative stress, altered immune pathways, perivascular fibrosis or a genetic predisposition [3, 12, 18]. A detailed overview of the pathways leading to specific forms of ILD is beyond the scope of this review, although some interesting findings are highlighted.

Endothelial dysfunction appears to play a central role, since the pulmonary vascular endothelium produces several important vasoactive mediators that modulate tone, smooth muscle cell proliferation and vascular remodelling [3]. Endothelin (ET)-1 is the most potent pulmonary vasoconstrictor and a co-mitogen for smooth muscle cells and fibroblasts [19]. Elevated endothelial production of ET-1 was detected in IPF, particularly in those with related PH [6]. Moreover, reports suggest that ET-1 also induces fibrogenesis *via* interaction with matrix metalloproteinases (pro-fibrotic) and initiates epithelial-to-mesenchymal transition *via* an ET type A receptor-mediated induction of transforming growth factor (TGF)-β1 [6]. The latter is one of the most potent pro-fibrotic growth factors and member of the TGF-β1 superfamily of cytokines which modulate many cellular functions including inflammatory response and cell proliferation/differentiation [12].

Bone morphogenetic protein receptor (BMPR)2 has a major role in suppressing TGF-β signalling and thus inhibiting the proliferation of vascular smooth muscle tissue and promoting the survival of pulmonary

arterial endothelium. BMPR2 levels are inversely correlated with mPAP in patients with IPF [6]. An inactivating mutation in the BMPR2 gene is the best-known cause of hereditary pulmonary arterial hypertension (PAH) [12]. Endothelin receptor antagonists, such as bosentan and macitentan, have been shown to reduce both the fibroproliferative damage and PH in rat models of pulmonary fibrosis [20]. Similar techniques were used to demonstrate a decrease in nitric oxide (NO) synthase in the lungs of patients with ILD, inversely proportional to the pathologic score [19]. NO is a potent vasodilator, but has also been shown to limit vascular remodelling, protect against reactive oxygen species and inhibit platelet aggregation [6, 19].

In IPF, repetitive injury of unknown origin leads to damage of alveolar epithelial cells and basement membranes, followed by exudation of fibrine and local fibroblast activation, finally resulting in fibrotic remodelling of lung parenchyma [9]. Unbalanced oxidative stress is an important underlying mechanism, more specifically a lack of the antioxidant glutathione [21]. This may lead to fibroproliferation (smooth muscle cells and increased production of extracellular matrix components) and antivasodilatory activities, explaining another link to PH. Moreover, soluble guanylyl cyclase is inactivated by oxidative stress and reconstitutes with antioxidants [22].

Vascular inflammation and pulmonary thromboembolism may contribute to the development of PH in patients with connective tissue disease associated ILD induced by autoimmune processes (*e.g.* anti-endothelial antibodies). Especially patients with diffuse systemic sclerosis (SScl) have a high risk of developing ILD and/or PH. Interestingly, whereas SScl patients with anticentromere antibodies have an increased risk of developing PAH (group 1), those with antiscleroderma 70 antibodies have a higher incidence of ILD and ILD-associated PH (group 3) [23].

In addition to its broad pro-inflammatory and immunological effects, the pleiotropic cytokine interleukin (IL)-6 is also an important driver of fibrosis. This role of IL-6 signalling has been observed in the bleomycin rat model of pulmonary fibrosis and the upregulated pathway is also detected in human PH patients [6]. There is a direct correlation between IL-6 and increased pulmonary pressures, vascular remodelling and RV remodelling through proliferative and anti-apoptotic mechanisms [6, 24]. Thus, it appears that the emergence of PH in ILD is a complex interplay of tissue destruction, inflammation, fibrosis and hypoxia, that exacerbate each other leading to pulmonary vascular remodelling through various pathways [10].

Detection of ILD-PH

Making the diagnosis of PH is often challenging, as many symptoms of PH mimic those of ILD (*e.g.* fatigue and exertional dyspnoea). There is no validated screening tool for PH in the setting of ILD [25]. Multimodality imaging such as echocardiography, computed tomography and ventilation perfusion scanning has emerged as an integral tool for screening, classifying and prognosticating in PH [26]. Clinical symptoms and signs tend to be nonspecific, until stigmata of right heart failure become apparent in later stages of the disease. Therefore, a high index of suspicion is needed, and screening for PH should be considered in patients with ILD where the severity of symptoms appears to be disproportionate to the parenchymal lung disease. Furthermore, certain findings concerning pulmonary function testing, circulating biomarkers, echocardiography and imaging may further contribute to a preliminary diagnosis of PH in patients with ILD, as illustrated in table 1.

First, with regard to pulmonary function testing, reduced diffusing capacity in the face of relatively preserved lung volumes, diminished exercise capacity and more impaired gas exchange at rest or during exercise than expected based on ventilatory impairments may suggest PH [4]. Secondly, biomarkers are increasingly used to discover ILD-PH. Elevated levels of brain natriuretic peptide (BNP) are sensitive, but lack specificity [4, 12]. For example, the plasma level of N-terminal proBNP is one of the components in the DETECT algorithm, which identify the subgroup of patients with SScl at risk of PH [23, 27]. Pre-clinical data suggest the diagnostic role of newer markers such as heart-type fatty acid binding protein and growth differentiation factor-15 as more specific molecules [12]. Thirdly, chest imaging (radiography and computed tomography) is also useful. The ratio of the diameter of the main pulmonary artery to that of the ascending aorta may predict PH in both COPD and ILD; a ratio >0.9 is predictive for a mPAP >20 mmHg, and a main pulmonary artery diameter at the level of the bifurcation >29 mm has a sensitivity of 89% and specificity of 83% for diagnosing PH [4, 15]. Other findings suggestive of PH on imaging include attenuation of the peripheral pulmonary vasculature and RV enlargement [3]. Using artificial intelligence may help to better provide mechanistic insights and improved phenotyping in ILD-PH [10].

TABLE 1 Findings suggestive for interstitial lung disease associated pulmonary hypertension

Clinical	Bimalleolar oedema Jugular venous distension Signs of RV dysfunction
Pulmonary function tests	Disproportionately severe decrease in diffusing capacity of the lung, while lung volumes are normal or only modestly reduced
6-min walk test	Lower than expected 6-min walk distance Marked exertional desaturation
Laboratory testing	Elevated (NT-pro)BNP Research: heart-type fatty acid binding protein, growth differentiation factor-15
Chest imaging	Increased pulmonary artery to ascending aorta ratio (>0.9) Main pulmonary artery diameter >29 mm RV enlargement
Echocardiography	Peak tricuspid regurgitation velocity $\geqslant$2.8 m·s^{-1} RV/LV basal diameter ratio >1.0 Flattening of the interventricular septum RV outflow Doppler acceleration time <105 ms and/or midsystolic notching Pulmonary artery diameter >25 mm Inferior vena cava diameter >21 mm with decreased inspiratory collapse Right atrial area >18 cm^2

RV: right ventricle; NT-proBNP: N-terminal pro-brain natriuretic peptide; LV: left ventricle.

Lastly, echocardiography is the most commonly used noninvasive detection tool for ILD-PH, although achieving a good signal of the tricuspid regurgitant jet velocity (TRV) can be challenging in patients with lung diseases. This measurement, combined with indirect measures of PH, such as RV function and pulmonary artery acceleration time, appear to be more accurate [4, 28]. Bax *et al.* [29] have developed and validated a stepwise echocardiographic score to predict severe ILD-PH even in patients without available TRV.

However, RHC remains the gold standard and is necessary to confirm the diagnosis of ILD-PH. Moreover, RHC should only be performed when the result will likely influence the management (*i.e.* listing for lung transplantation, inclusion in clinical trials or initiation of pulmonary vasoactive therapy), given the invasive nature of the procedure [1, 4, 10]. The haemodynamic definition of PH, in the context of chronic lung disease (group 3 PH) was updated in the 6th World Symposium on Pulmonary Hypertension to include a resting mPAP of >20 mmHg, a pulmonary artery occlusion pressure $\leqslant$15 mmHg and a pulmonary vascular resistance of $\geqslant$3 Wood Units [1, 4]. Keep in mind that this definition does not distinguish between group 3 and group 1 PH; the distinction is made relying on defining the lung disease as the primary driver [10].

Treatment

Currently, there is no approved medical therapy for ILD-PH. The underlying lung disease should be optimally treated according to current guidelines, including supplemental long-term oxygen therapy if needed [1]. Reversible causes such as chronic thromboembolic PH and sleep disordered breathing require special attention and treatment. Due to age and comorbidities, only a minority of ILD patients are eligible for lung transplantation. Diuretics should be used to optimise fluid balance and patients should be referred for pulmonary rehabilitation. Recently approved antifibrotic medications for IPF and progressive fibrosing ILD (nintedanib and pirfenidone) have shown improvement in forced vital capacity (FVC) and reduced disease progression; however, the impact on PH was not studied [30, 31].

Pharmacological agents used for patients with group 1 PH (PAH) can be divided into five categories using three different pathways: prostacyclin pathway (prostacylins, prostacyclin receptor agonists), NO pathway moderators (phosphodiesterase (PDE)-5 inhibitors, NO-cGMP enhancers) and endothelin receptor antagonists. The pivotal trials set exclusion criteria concerning pulmonary function testing (*e.g.* total lung capacity <60–70% predicted). However, these agents have also been analysed in patients with ILD-PH, although mostly in unblinded case series or registry data, and have shown inconsistent results. Randomised controlled trials in these patient populations are summarised in table 2.

Interfering with the NO pathway in ILD-PH using PDE-5 inhibitors was tested first. In the randomised controlled STEP-IPF trial, 180 patients received either sildenafil, a PDE-5 inhibitor, or placebo for

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TABLE 2 Overview of double-blind, placebo-controlled, randomised clinical trials evaluating different classes of pulmonary arterial hypertension drugs in patients with idiopathic pulmonary fibrosis (IPF) and/or interstitial lung disease (ILD)

	Trial	Patient population	Main inclusion criteria	Intervention	Primary end-point	Results
PDE-5 inhibitors	STEP-IPF trial [32]	180: 89 sildenafil 91 placebo	IPF at an advanced stage (D_{LCO} <35% predicted)	Sildenafil *versus* placebo for 12 weeks	Proportion of patients with ⩾20% increase on 6MWT	☒ 10% (sildenafil) *versus* 7% (placebo) (p=0.39)
Soluble guanylate cyclase stimulators	RISE-IIP trial [33]	147: 73 riociguat 74 placebo	IIP FVC >45% 6MWD 150–450 m WHO functional classes II–IV Pre-capillary PH confirmed by RHC SBP >95 mmHg No signs or symptoms of hypotension	Riociguat *versus* placebo for 26 weeks	Change from baseline in 6MWT	☒ Study terminated early due to increased adverse events
Endothelin receptor antagonists	BPHIT trial [34]	60: 40 bosentan 20 placebo	IIP Pre-capillary PH confirmed by RHC	Bosentan *versus* placebo for 16 weeks	Fall from baseline PVRI ⩾20%	☒ 28.0% (bosentan) *versus* 28.6% (placebo) (p=0.97)
	ARTEMIS-IPF trial [35]	494: 330 ambrisentan 164 placebo	Patients with IPF with minimal or no honeycombing on high-resolution computed tomography scan	Ambrisentan *versus* placebo	Time to IPF disease progression	☒ 27.4% (ambrisentan) *versus* 17.2% (placebo) (p=0.01); trial terminated early due to increased disease progression in intervention group
	MUSIC trial [36]	178: 119 macitentan 59 placebo	IPF of <3 years' duration A histological pattern of usual interstitial pneumonia on surgical lung biopsy	Macitentan *versus* placebo for 12 months	Change from baseline in FVC	☒ −0.2 L (macitentan) *versus* −0.2 L (placebo) (p=1.00)
Prostanoids	INCREASE trial [37]	326: 163 inhaled treprostinil 163 placebo	ILD and pre-capillary PH confirmed by RHC 6MWT >100 m	Treprostinil *versus* placebo for 16 weeks	Change from baseline in distance on 6MWT	☑ +21.1 m (treprostinil) *versus* −10.0 m (placebo) (p<0.001)
PDE-5 inhibitors on top of approved IPF therapy	INSTAGE trial [38]	273: 137 nintedanib +sildenafil 136 nintedanib +placebo	IPF at an advanced stage (D_{LCO} <35% predicted)	Nintedanib+sildenafil *versus* nintedanib +placebo for 24 weeks	Change from baseline in the total score on the SGRQ at week 12	☒ −1.28 *versus* −0.77 points (p=0.72)
	Efficacy and safety of sildenafil added to pirfenidone in patients with advanced IPF and risk of PH [16]	177: 88 pirfenidone +sildenafil 89 pirfenidone +placebo	IPF at an advanced stage (D_{LCO} <40% predicted) mPAP ⩾20 mmHg with PAWP ⩽15 mmHg on RHC or intermediate/high probability of group 3 PH on echocardiography	Pirfenidone+sildenafil *versus* pirfenidone +placebo for 52 weeks	Proportion of patients with disease progression	☒ 73% (sildenafil) *versus* 70% (placebo) (p=0.65)

PDE: phosphodiesterase; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-min walk test; IIP: idiopathic interstitial pneumonia; FVC: forced vital capacity; 6MWD: 6-min walk distance; WHO: World Health Organization; PH: pulmonary hypertension; RHC: right heart catheterisation; SBP: systolic blood pressure; PVRI: pulmonary vascular resistance index; SGRQ: St George's Respiratory Questionnaire; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; ☒: negative trial; ☑: positive trial.

12 weeks. There was no significant difference in functional outcome; however, some improvement in shortness of breath and quality of life was noticed and there were no significant side-effects [38]. The combination of sildenafil in addition to the antifibrotic drug nintedanib has been tested in the INSTAGE trial in patients with IPF. Although this combination did not improve quality of life, patients who had been treated with nintedanib plus sildenafil had a lower risk of reaching the pre-specified composite end-point of an absolute decline in the FVC of ⩾5% pred value or death than did those who received treatment with nintedanib alone (hazard ratio 0.56, 95% CI 0.38–0.82) [4, 38]. Unfortunately, these positive results were not confirmed in the recently presented trial by Behr *et al*. [16] testing sildenafil as add-on therapy to pirfenidone as judged by disease progression and changes in pulmonary function tests, exercise capacity or health-related quality of life up to 52 weeks. Concerning the NO-cGMP enhancers, the largest trial to date (RISE-IIP) evaluated riociguat, a soluble guanylate cyclase stimulator, in a patient population with group 3 PH due to idiopathic interstitial pneumonia (IIP) and was stopped early owing to serious harm, including increased serious adverse events and mortality [33]. Therefore, the investigators of this phase 2b study concluded that riociguat should not be used in patients with PH associated with IIP. A *post hoc* analysis of the RISE-IIP study examining high-resolution computed tomography data suggested that patients with more emphysema than fibrosis had worse outcomes, and this may have at least partly driven the unfavourable outcome of the trial [39].

Several studies have investigated the use of endothelin receptor antagonists in ILD-PH, all of which have shown no benefit [4, 34, 35, 40]. The BPHIT trial showed no difference in invasive pulmonary haemodynamics, functional capacity or symptoms between the bosentan and placebo groups over 16 weeks [34]. There were no serious safety alerts in this trial. Ambrisentan was even linked with an increased risk for disease progression and respiratory hospitalisations in the early-terminated ARTEMIS-IPF trial [35]. A single-group open-label trial of macitentan for patients with scleroderma-associated ILD and PH is ongoing (www.clinicaltrials.gov identifier NCT03726398).

Lastly, studies investigating the safety and efficacy of continuous intravenous infusion of prostacyclin (epoprostenol) in ILD-PH are limited to several small case series [4]. The inconsistent conclusions could be a result of the theoretical concern that systemic administration of vasomodulating agents can worsen ventilation–perfusion mismatching due to increased intrapulmonary shunting, thus aggravating hypoxaemia and worsening disease progression [10, 37, 41]. Intrapulmonary administration of PAH drugs by inhalation could address this issue, in which active agents only become available in best-ventilated lung units [3, 37].

In the recently published INCREASE trial from Waxman *et al.* [37], patients with ILD-PH treated with inhaled treprostinil had significant improvements in exercise capacity (the primary efficacy end-point), as shown by clinically relevant changes in the 6-min walk distance from baseline to week 16 between the two groups. In addition, clinical worsening occurred less frequently in the treprostinil group as compared with the placebo group. Treprostinil is an analogue of prostacyclin, which promotes direct vasodilation of arterial vascular beds and inhibits platelet aggregation [37]. Its recent approval by the United States Food and Drug Administration as the first therapeutic option for this patient population is an important step [10]. A phase 3 clinical trial to assess pulsed inhaled nitric oxide (iNO) in subjects with pulmonary fibrosis at risk of PH is currently ongoing (www.clinicaltrials.gov identifier NCT03267108). Short-term treatment with pulsed NO in combination with oxygen showed promising results in patients with COPD and PH [42]. Phase 2b/3 trials concerning iNO demonstrated improved participants' self-reported quality of life, lowered their shortness of breath and were generally safe and well-tolerated [43]. Large, long-term trials, focusing on composite clinical primary end-points such as hospitalisations, indications of disease progression and death are eagerly awaited [44].

The population of group 3 PH patients is highly heterogeneous, since it includes subjects with different lung diseases (ILD, COPD and sleep disordered breathing) and various stages. Moreover, patients with ILD lie in a vast spectrum of underlying pathogenic mechanisms and PH severity, implicating that selection criteria (*e.g.* morphologic phenotyping and disease burden) and optimal staging could be the key to positive results [41]. Furthermore, shifting from medication with a predominantly vasodilator effect towards evaluation of innovative drugs that target vascular remodelling is also of interest [30].

Conclusion

PH is an under-recognised entity in patients with ILD and adversely affects functional capacity and survival. The diagnosis is challenging, a high index of suspicion is needed, and no recommendation exists regarding which patients to screen or the optimal method of doing so. RHC remains the gold standard for a definitive diagnosis, but is only necessary when it is likely to alter the management strategy. The treatment of ILD-PH is clearly an area of unmet clinical need. The recently published INCREASE trial, with

treatment with inhaled treprostinil, shows encouraging results. Future trials focusing on composite clinical primary end-points such as hospitalisations, disease progression and death are eagerly awaited. Further unravelling of the pathogenesis of ILD-PH, and the role of the vasculature in particular, has the potential to unlock new therapeutic opportunities.

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