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Early View

Review

Pulmonary Hypertension in Interstitial Lung Disease: An area of unmet clinical need

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Please cite this article as: Dhont S, Zwaenepoel B, Vandecasteele E, *et al*. Pulmonary Hypertension in Interstitial Lung Disease: An area of unmet clinical need. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00272-2022).

Pulmonary Hypertension in Interstitial Lung Disease:

An area of unmet clinical need

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Take home message: Pulmonary hypertension is an underrecognized entity in patients with interstitial lung disease and adversely affects clinical outcomes. Newer therapeutic strategies such as intrapulmonary administration of pulmonary vasodilators show encouraging results, making it worthwhile to set the diagnosis.

Keywords: Pulmonary hypertension, interstitial lung diseases, idiopathic pulmonary fibrosis, right heart catheterization

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 catheterization 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 hypoxemia 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, unraveling 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), chronic obstructive pulmonary disease (COPD) and sleep-disordered breathing (e.g. obstructive sleep apnea 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 catheterization (RHC): a resting mean pulmonary artery pressure (mPAP) above 20 mm Hg 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.[2, 4–6] 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.[7] 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.[8]

Despite its impact, there is no consensus regarding screening for PH in ILD. Early detection of PH-ILD depends on the clinical suspicion of the treating physician and confirming the diagnosis is often challenging. Until now, treatment is 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 - mainly idiopathic pulmonary fibrosis (IPF)- related pulmonary hypertension and its prevalence, pathophysiology, diagnosis, and treatment.

Interstitial lung diseases

ILD is an umbrella term for a heterogeneous group of more than 150 lung diseases with common functional characteristics (restrictive physiology and impaired gas exchange), but with a wide range of causes, pathological and clinical manifestations, imaging characteristics, and variable outcomes.[9] 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, idiopathic pulmonary fibrosis (IPF) and some other ILDs are characterized 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 (pf-ILD) are associated with a cascade of clinical consequences including exercise intolerance, respiratory failure, increasing oxygen requirements and eventually death.[10, 11]

Idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonitis, connective tissue disease related ILD, sarcoidosis, and pulmonary Langerhans cell histiocytosis are the ILDs most commonly associated with PH.[3, 9, 12] Importantly, sarcoidosis and Langerhans cell histiocytosis related PH are classified in group 5 (PH due to other causes) due to their multifactorial pathophysiology.[13] For example, mechanisms of sarcoidosis-associated PH mainly include hypoxemia from ILD, vascular disease, mediastinal distortion/compression from lymphadenopathy, and extrapulmonary disease manifestations (e.g., left ventricular dysfunction).[14]

Most of the data on PH in patients with ILD originates from the literature concerning

IPF. In general, PH in patients with ILD is mild to moderate, rarely severe. In a large trial in patients with IPF, 46% of patients with advanced ILD had mPAP > 25 mm Hg, but only 9% had mPAP > 40 mm Hg.[8] 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 operator characteristic (ROC) analysis suggested a mPAP of 17 mm Hg as the best discriminator of mortality.[15, 16] The reported prevalence of IPF ranges from 14 to 43 per 100,000 persons and PH is detected in up to 30 to 50 percent of this patient group.[13] The incidence of IPF increases with older age, with presentation typically occurring in the sixth and seventh decades.[16] As to the outcome, PH is associated with a three-fold increase in mortality compared with people with pulmonary disease and no PH.[17] However, according to the COMPERA registry, there is no difference in survival between the different types of ILD associated with PH.[4, 18]

Pathogenesis of ILD related PH

The high co-incidence of ILD and PH can be explained by shared pathophysiology concerning parenchymal and vascular remodeling, as conceptualized 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 is emerging data that the vasculature itself plays a pathogenic role in the incitement of lung diseases.[19] Alveolar hypoxia is well known to cause reactive vasoconstriction (the Euler-Liljestrand reflex) and 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 remodeling.[20] Nevertheless, PH has been noted to occur in the absence of resting hypoxemia or advanced pulmonary disease and there is a lack of correlation between mPAP and the degree of abnormalities in pulmonary function testing (PFT).[3] Other mechanisms

leading to PH in ILD include endothelial dysfunction, oxidative stress, altered immune pathways, perivascular fibrosis or a genetic predisposition.[3, 13, 19] A detailed overview of the pathways leading to specific forms of ILD, is behind 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 remodeling.[3] Endothelin-1 (ET-1) is the most potent pulmonary vasoconstrictor and a co-mitogen for smooth muscle cells and fibroblasts.[20] Elevated endothelial production of ET-1 was detected in IPF, particularly in those with related PH.[7] Moreover, reports suggest that ET-1 also induces fibrogenesis via interaction with matrix metalloproteinases (profibrotic) and initiates epithelial to mesenchymal transition via an ET type A receptor-mediated induction of Transforming growth factor beta 1(TGF-β1). [7] The latter is one of the most potent profibrotic growth factors and member of the TGF-β1superfamily of cytokines which modulate many cellular functions including inflammatory response and cell proliferation/differentiation [13].

Bone morphogenetic protein receptor 2 (BMPR2) has a major role in suppressing TGF-β signaling and thus inhibiting the proliferation of vascular smooth muscle tissue and promoting the survival of pulmonary arterial endothelial. BMPR2 levels are inversely correlated with mPAP in patients with IPF. [7] An inactivating mutation in the BMPR2 gene is the best-known cause of hereditary pulmonary arterial hypertension.[13] 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.[21] 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.[20] NO is a potent vasodilator, but has also been shown to limit vascular remodeling, protect against reactive oxygen species and inhibit platelet aggregation.[7, 20]

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 remodeling of lung parenchyma.[10] Unbalanced oxidative stress is an important underlying mechanism, more specifically a lack of the antioxidant glutathione.[22] This may lead to fibroproliferation (smooth muscle cells and increased production of ECM components) and anti-vasodilatory activities, explaining another link to PH. Moreover, soluble guanylyl cyclase (sGC) is inactivated by oxidative stress and reconstitutes with antioxidants.[23]

Vascular inflammation and pulmonary thrombo-embolism 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 to develop ILD and/or PH. Interestingly, whereas SScl patients with anti-centromere antibodies have an increased risk to develop PAH (group 1), those with anti-scleroderma 70 antibodies have a higher incidence of ILD and ILD-associated PH (group 3).[24]

In addition to its broad pro-inflammatory and immunologic effects, the pleiotropic cytokine IL-6 is also an important driver of fibrosis. This role of IL-6 signaling has been observed in the bleomycin rat model of pulmonary fibrosis and the upregulated pathway is also detected in human PH patients.[7] There is a direct correlation between IL-6 and increased pulmonary pressures, vascular remodeling and RV remodeling through proliferative and anti-apoptotic mechanisms.[7, 25] 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 remodeling through various pathways.[11]

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 dyspnea). There is no validated screening tool for PH in the setting of ILD.[26] Multimodality imaging such as echocardiography, computed tomography, and ventilation perfusion scans has emerged as an integral tool for screening, classifying and prognosticating in PH. [27] 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 PFT, circulating biomarkers, echocardiography and imaging may further contribute to a preliminary diagnosis of PH in patients with ILD as illustrated in *Table 1*.

First, as to PFT, 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, 13] The plasma level of N-terminal brain natriuretic prohormone BNP (NT-proBNP) is for example one of the components in the DETECT algorithm, which identify the subgroup of patients with SScl at risk of PH.[24, 28] Preclinical 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.[13] Thirdly, chest imaging (X-ray and computed tomography) is also useful. The ratio of the main pulmonary artery to ascending aorta diameter may predict PH in both COPD and ILD; a ratio above 0,9 is predictive for a mPAP > 20 mmHg and a main pulmonary artery diameter at the level of the bifurcation above 29 mm has a sensitivity of 89% and specificity of 83% for

diagnosing PH.[4, 16] Other findings suggestive of PH on imaging include attenuation of the peripheral pulmonary vasculature and a right ventricular enlargement.[3] Using artificial intelligence may help to better provide mechanistic insights and improved phenotyping in ILD-PH.[11]

Last, echocardiography is the most commonly used non-invasive detection tool for PH-ILD, although achieving a good signal of the tricuspid regurgitant jet (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, 29] Recently, Bax *et al*. developed and validated a stepwise echocardiographic score to predict severe PH-ILD even in patents without available TRV. [30]

However, right heart catheterization 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.[4, 5, 11] The hemodynamic 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 mean pulmonary artery pressure of > 20 mm Hg, a pulmonary artery occlusion pressure ≤ 15 mm Hg, and a pulmonary vascular resistance of ≥ 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.[11]

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.[5] Reversible causes such as chronic thromboembolic

pulmonary hypertension 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 optimize fluid balance and patients should be referred to pulmonary rehabilitation. Recently approved antifibrotic medications for IPF and progressive fibrosing ILD - nintedanib and pirfenidone – showed improvement in FVC and reduced disease progression, however, the impact on PH was not studied.[31, 32]

Pharmacological agents used for patients with group 1 PH (pulmonary arterial hypertension) can be divided into five categories using three different pathways: prostacyclin pathway (prostacylins, prostacycline receptor agonists), NO pathway moderators (PDE5-inhibitors, NO-cGMP enhancers) and endothelin receptor antagonists. The pivotal trials set exclusion criteria concerning pulmonary function testing (e.g., TLC < 60-70% of predicted). However, these agents have also been analyzed in patients with ILD-PH, though mostly in unblinded case series or registry data, and have shown inconsistent results. Randomized controlled trials in these patient populations are summarized in *Table 2*.

Interfering with the NO pathway in ILD-PH using PDE-5 inhibitors was tested first. In the randomized controlled STEP-IPF trial, 180 patients received either sildenafil, a PDE-5 inhibitor, or placebo for 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.[33] 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 prespecified composite end point of an absolute decline in the FVC of at least 5 percentage points of the predicted value or death than did those who received treatment with nintedanib alone (HR 0.56; 95% CI 0.38 - 0.82).[4, 34] Unfortunately, these positive results were not confirmed in the recently presented trial by Behr

et al. 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.[17] 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.[35] 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 (HRCT) data suggested that patients with more emphysema than fibrosis had worse outcome and this may have at least partly driven the unfavorable outcome of the trial. [36]

Several studies have investigated the use of endothelin receptor antagonists in ILD-PH, all of which have shown no benefit.[4, 37–40] The B-PHIT trial showed no difference in invasive pulmonary hemodynamics, functional capacity, or symptoms between the bosentan and placebo groups over 16 weeks. [40] There were no serious safety alerts in this trial. Ambrisentan was even linked with an increased risk for disease progression and respiratory hospitalizations in the early terminated ARTEMIS-IPF trial.[38] A single-group open-label trial on macitentan for patients with scleroderma-associated ILD and PH is ongoing (NCT03726398).

Lastly, studies investigating the safety and efficacy of continuous intravenous infusion of prostacyclin (epoprostenol) in PH-ILD 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 hypoxemia and worsening disease progression.[11, 41, 42] Intrapulmonary administration of PAH drugs by inhalation could

address this issue, in which active agents only become available in best-ventilated lung units.[3, 41]

In the recently published INCREASE-trial from Waxman and colleagues, 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-minute walk distance from baseline to week 16 between the two groups.[41] 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.[41] Its recent approval by the Food and Drug Administration as the first therapeutic option for this patient population is an important step.[11] A phase 3 clinical trial to assess pulsed inhaled nitric oxide (iNO) in subjects with pulmonary fibrosis at risk for pulmonary hypertension is currently ongoing (NCT03267108). Short-term treatment with pulsed NO in combination with oxygen showed promising results in patients with COPD and pulmonary hypertension. [43] Phase 2b/3 trials concerning iNO demonstrated improved participants' self-reported quality of life, lowered their shortness of breath, and was generally safe and well-tolerated. [44]. Large, long-term trials, focusing on composite clinical primary endpoints such as hospitalizations, indications of disease progression, and death are eagerly awaited.[45]

The population of group 3 PH patients is highly heterogenous, 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.[42] Furthermore, shifting from medication with a predominantly vasodilator effect towards evaluation of innovative drugs that target vascular remodeling also of interest. [30]

Conclusion

Pulmonary hypertension is an underrecognized 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. Right heart catheterization remains the gold standard for a definitive diagnosis but is only necessary when it's 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 endpoints such as hospitalizations, disease progression, and death are eagerly awaited. Further unraveling of the pathogenesis of ILD-PH, and the role of the vasculature in particular, has the potential to unlock new therapeutic opportunities.

Points for clinical practice

- 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 catheterization 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.

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 endpoints such as patient reported outcomes, quality of life, hospitalizations and survival are eagerly awaited.
- Further unraveling of the pathogenesis of ILD-PH has the potential to unlock new therapeutic opportunities.

Declarations

Ethics approval and consent to participate: not applicable

Consent for publication: not applicable

Availability of data and materials: not applicable

Competing interests: The authors declare that they have no competing interests

Funding: none

Tables and figures

TEST	FINDINGS
CLINICAL	• Bimalleolar edema • Jugular venous distension • Signs of right ventricle dysfunction
PULMONARY FUNCTION TESTS	• Disproportionately severe decrease in diffusing capacity of the lung, while lung volumes are normal or only modestly reduced.
SIX-MINUTE WALK TEST	• Lower than expected six-minute 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 ≥ 2,8 m/s • 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 cava diameter > 21 mm with decreased inspiratory collapse • Right atrial area > 18 cm^2

Table 1 Findings suggestive for ILD-associated pulmonary hypertension (ILD-PH)

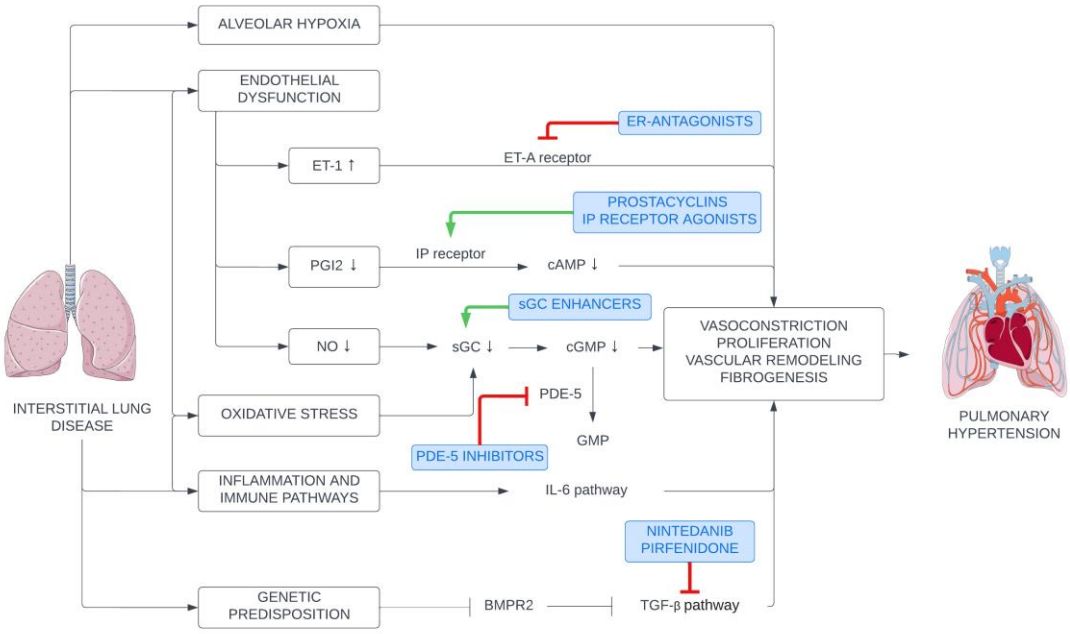
Abbreviations: LV: left ventricle. (NT-pro)BNP: (N-terminal prohormone) Brain Natriuretic Peptide. RV: right ventricle.

DRUG CLASS	TRIAL	PATIENT POPULATION	MAIN INCLUSION CRITERIA	INTERVENTION	PRIMARY ENDPOINT	RESULTS
PDE-5 inhibitors	**STEP-IPF trial** *NEJM, 2013*	180 - 89 sildenafil - 91 placebo	IPF in an advanced stage (= DLCO < 35% of the predicted value)	Sildenafil vs. placebo for 12 weeks	Proportion of patients with ≥ 20% increase on 6MWT	☒ 10% (sildenafil) vs. 7% (placebo) (P = 0.39)
Soluble guanylate cyclase stimulators	**RISE-IIP trial** *Lancet Respir Med, 2019*	147 - 73 riociguat - 74 placebo	- idiopathic interstitial pneumonia - FVC > 45% - 6MWT 150-450 m - WHO functional classes II-IV - precapillary pulmonary hypertension confirmed by right heart catheterization - SBP > 95 mm Hg - no signs or symptoms of hypotension	Riociguat vs. placebo for 26 weeks	Change from baseline in 6MWT	☒ Study terminated early due to increased adverse events
Endothelin receptor antagonists	**BPHIT trial** *Am J Respir Crit Care Med, 2014*	60 - 40 bosentan - 20 placebo	- idiopathic interstitial pneumonia - precapillary pulmonary hypertension confirmed by right heart catheterization	Bosentan vs. placebo for 16 weeks	Fall from baseline PVRi ≥ 20%	☒ 28.0% (bosentan) vs. 28.6% (placebo) (P = 0.97)
	ARTEMIS-IPF trial *Annals of Internal Medicine, 2013*	494 - 330 ambrisentan - 164 placebo	Patients with IPF with minimal or no honeycombing on high-resolution computed tomography scan	Ambrisentan vs. placebo	Time to IPF disease progression	☒ 27.4% (ambrisentan) vs. 17.2% (placebo) (P = 0.01) – trial terminated early due to increased disease progression in intervention group
	MUSIC trial *Eur Respir J, 2013*	178 - 119 macitentan - 59 placebo	- IPF of < 3 years duration - a histological pattern of usual interstitial pneumonia on surgical lung biopsy	Macitentan vs. placebo for 12 months	Change from baseline in FVC	☒ - 0.2L (macitentan) vs. – 0.2L (placebo) (P = 1.00)
Prostanoids	**INCREASE trial** *NEJM, 2021*	326 - 163 inhaled treprostinil - 163 placebo	- ILD and precapillary pulmonary hypertension confirmed by right heart catheterization - 6MWT > 100m	Treprostinil vs. placebo for 16 weeks	Change from baseline in distance on 6MWT	☑+ 21.1m (troprostinil) vs. – 10.0m (placebo) (P < 0.001)
PDE-5 inhibitors on top of approved IPF-therapy	**INSTAGE trial** *NEJM, 2018*	273 - 137 nintedanib + sildenafil - 136 nintedanib + placebo	IPF in an advanced stage (= DLCO < 35% of the predicted value)	Nintedanib + Sildenafil vs. Nintedanib + placebo for 24 weeks	Change from baseline in the total score on the SGRQ at week 12	☒ −1.28 vs −0.77 points (P = 0.72)
	Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension *Lancet Respir Med, 2021*	177 - 88 pirfenidone + sildenafil - 89 pirfenidone + placebo	- IPF in an advanced stage (= DLCO < 40% of the predicted value) - mPAP ≥20 mmHg with PAWP ≤15 mmHg on right-heart catheterization OR intermediate/high probability of group 3 PH on echocardiography	Pirfenidone + sildenafil vs. pirfenidone + placebo for 52 weeks	Proportion of patients with disease progression	☒ 73% (sildenafil) vs. 70% (placebo) (P = 0.65)

Table 2 Overview of double-blind, placebo-controlled, randomized clinical trials evaluating different classes of pulmonary arterial hypertension (PAH) drugs in patients with idiopathic pulmonary fibrosis (IPF) and/or Interstitial Lung Disease (ILD).

Abbreviations: 6MWT: 6-minute-walking-test. DLCO: diffusing capacity of the lung for carbon monoxide. FVC: forced vital capacity. ILD: interstitial lung disease. IPF: idiopathic pulmonary fibrosis. mPAP: mean pulmonary artery pressure. PAWP: pulmonary artery wedge pressure. PDE-5: phosphodiesterase type 5. PH: pulmonary hypertension. PVRi: pulmonary vascular resistance index. SBP: systolic blood pressure. SGRQ: St. George's Respiratory Questionnaire.

Figure 1


ALVEOLAR HYPOXIA
ENDOTHELIAL DYSFUNCTION
ER-ANTAGONISTS
ET-A receptor
ET-1 ↑
PROSTACYCLINS
IP RECEPTOR AGONISTS
IP receptor
PGI2 ↓
cAMP ↓
sGC ENHANCERS
NO ↓
sGC ↓
cGMP ↓
VASOCONSTRICTION
PROLIFERATION
VASCULAR REMODELING
FIBROGENESIS
INTERSTITIAL LUNG DISEASE
OXIDATIVE STRESS
PDE-5
GMP
PDE-5 INHIBITORS
INFLAMMATION AND IMMUNE PATHWAYS
IL-6 pathway
NINTEDANIB
PIRFENIDONE
GENETIC PREDISPOSITION
BMPR2
TGF-β pathway
PULMONARY HYPERTENSION

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