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INTERSTITIAL LUNG DISEASE (G TINO, SECTION EDITOR)

Pulmonary hypertension in idiopathic pulmonary fibrosis: epidemiology, diagnosis and therapeutic implications

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Abstract A significant proportion of patients with idiopathic pulmonary fibrosis have concurrent pulmonary hypertension. In most, elevations in pulmonary pressures are modest, but approximately 10 % have disproportionately elevated pulmonary pressures. Pulmonary hypertension is associated with decreased functional status and increased mortality. The etiology remains incompletely understood, but likely involves a complex interplay of abnormal angiogenesis, vascular ablation, remodeling, and vasoconstriction. Transthoracic echocardiogram, six-minute walk testing, pulmonary function testing and biomarkers may suggest pulmonary hypertension, but none are sensitive or specific enough to rule in or exclude the diagnosis. Right heart catheterization remains the diagnostic gold standard. Supplemental oxygen should be provided if required and sleep-disordered breathing should be addressed. Small trials suggest that vasodilator therapy may improve exercise tolerance, but no mortality benefit has been demonstrated. Patients with disproportionate pulmonary hypertension should be encouraged to enroll in clinical trials of vasodilator therapy so that the role of these agents can be better defined. Ultimately, genetic profiling technology may serve to individualize therapy in such patients.

Keywords Idiopathic pulmonary fibrosis · Pulmonary hypertension · Interstitial lung disease · Chronic lung disease

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Introduction

The Idiopathic Pulmonary Fibrosis Clinical Research Network recently published the results of the PANTHER-IPF trial, a study designed to assess the efficacy of the combination of prednisone, azathioprine, and N-acetylcysteine in patients with idiopathic pulmonary fibrosis (IPF). The trial was halted early due to an increased rate of death in the treatment group [1]. This study represents the most recent disappointment in the search for a medical therapy for IPF, a progressive fibrotic disorder of the lungs of unknown cause, with no universally recognized effective medical therapy. IPF affects between 14 and 43 per 100,000 persons in the United States and has a dismal prognosis, with an estimated median survival of 2.5 to 5 years from the time of diagnosis [2].

While effective medical therapies for IPF remain elusive, significant progress has been made in the understanding of the various phenotypic presentations of the disease and the underlying pathophysiology of each. One key phenotype that holds potential for possible therapeutic inroads is that of IPF with associated pulmonary hypertension (PH). Aside from the possibility of the development of novel therapies for this specific IPF phenotype, recognition of PH in IPF is essential, as associated PH negatively affects functional status and outcomes [3]. In this article, we will review the medical literature on the epidemiology, pathophysiology, and optimal diagnostic and therapeutic approach to PH in IPF.

Definition

The most recent clinical consensus guidelines on PH were derived during the World Symposium on Pulmonary Hypertension held in Dana Point, CA, USA in 2008. These guidelines define PH as a resting mean pulmonary artery pressure (mPAP)≥25 mmHg, assessed by right heart catheterization (RHC) [4]. PH associated with IPF is categorized as group 3: "Pulmonary hypertension due to lung diseases and/or hypoxia." Of note, the diagnosis of PH based on an mPAP≥30 mmHg during exercise is not supported by the current guidelines, which cite a lack of published data to support this definition. Patients with mPAP≥40 mmHg are characterized as "out-of-proportion" PH, and likely represent a distinct phenotype from patients with more modest elevations in mPAP [4].

While the guidelines help to standardize definitions for the purpose of research, these definitions may fail to capture all clinically important effects of pulmonary hemodynamics in IPF. For instance, a lower mPAP than required for a diagnosis of PH may be clinically significant. Hamada and colleagues prospectively followed a group of 61 IPF patients with RHC data from the time of diagnosis up to a maximum of 14 years. They found that a mPAP threshold of >17 mmHg was associated with significantly worsened 5 year survival (62.2 % vs. 16.7 %, $p<0.001$) [5]. Additionally, although data on pulmonary artery pressures (PAP) during exercise are somewhat limited, exercise-induced changes in PAP in IPF appear to have significant implications [6, 7]. Weitzenblum et al. assessed hemodynamics and arterial blood gas readings in 31 patients with IPF. They found an increase in mPAP from 21.7±7.8 mmHg to 45.3±16.2 mmHg and a drop in partial pressure of arterial oxygen (PaO_2) from 69.6±11.6 mmHg to 56.0±9.4 mmHg with exercise [8]. While the guidelines fail to recognize exercise-induced PH as a distinct pathological phenomenon, further research is required to determine the clinical significance of this entity.

Prevalence

The prevalence of PH in IPF is poorly defined, with reports in the literature ranging from as low as 8.1 % to as high as 86.4 % [5, 9–23]. Table 1 summarizes the available studies and their characteristics. There are numerous reasons for the significant disparities between studies. One reason is the methodology used to determine PH. Transthoracic echo (TTE) appears to be unreliable for the diagnosis of PH in IPF, so prevalence data obtained with TTE may be inaccurate [17, 24]. Another issue is the nature of the study populations. The bulk of the data obtained via RHC has been performed in patients referred for evaluation for lung transplantation. Patients within these cohorts are likely younger, have fewer comorbidities, and may have more severe respiratory disease than patients not referred for transplant evaluation. Finally, significant variability in pulmonary pressures may exist depending on the timing of assessment in the disease process. This was demonstrated in a cohort of 44 patients with serial measurements of PAP by Nathan et al. Only 38.6 % of these patients had PH at baseline assessment, but 86.4 % had PH by the time of transplant [18]. The prevalence of disproportionate PH is even less well defined, with reports ranging from 9.0 % to 31.0 % [16, 23, 25]. Further study is required to determine the prevalence and predictors of disproportionate PH.

Impact of PH in IPF

Exercise capacity

A lower six-minute-walk distance (6MWD) has been associated with decreased survival in IPF [12]. Numerous studies have demonstrated an association between PH and decreased 6MWD [13, 16, 22, 23]. Lettieri et al. compared patients with and without PH as assessed by RHC and found a statistically significant decrease in both 6MWD (143.5±65.5 m vs. 365.9±81.8 m, $p<0.001$) and mean pulse oximetric saturation nadir during six-minute-walk test (6MWT) (80.1±3.7 % vs. 88.0±3.5 %, $p<0.001$) [13]. Boutou and colleagues performed cardiopulmonary exercise testing on 81 patients with IPF. They found that a systolic pulmonary artery pressure (PASP)>35 mmHg on TTE was associated with a decreased maximum work rate achieved and peak oxygen consumption ($VO2_{max}$) in comparison to patients without PH [21]. Based on these studies, it appears that PH significantly impacts exercise tolerance in a negative fashion.

Effect of transplantation outcomes

The effect of secondary PH in IPF patients on transplantation outcomes is an area of debate due to heterogeneity in study outcomes and the limitations of available studies. Although some studies have found no impact of PH on outcomes [26–28], there is evidence that preoperative PH may increase the risk of death following single lung transplantation in IPF [29]. Additionally, other studies have demonstrated an increased risk for primary graft dysfunction in the context of pre-existing PH [30, 31].

Mortality

PH has consistently been demonstrated to adversely affect survival in IPF [9, 13]. Nadrous et al. demonstrated a negative correlation between survival and PASP on TTE with median survival rates of 4.8, 4.1, and 0.7 years for patients with

Table 1 Studies reporting prevalence data on pulmonary hypertension in IPF

Study	Patient Number	Patient Population	PH Definition	% with PH	% with severe PH	Comments
King et al. 2001 [9]	238	Enrolled in prospective study at referral center	Radiographic evidence of PH on CXR	20.0 %	Not reported	Presence of PH on CXR associated with increased mortality
Agarwal et al. 2005 [10]	25	Referral center	sPAP>40 mmHg by TTE	36.0 %	Not reported	Symptomatic patients excluded
Nadrous et al. 2005 [11]	88	Initial evaluation at referral center	sPAP>35 mmHg by TTE; Severe PH=sPAP >50 mmHg by TTE	84.0 %	31.0 %	Worsened survival when SPAP>50 mmHg
Lederer et al. 2006 [12]	376	Review of patients listed for transplant on UNOS	mPAP>25 mmHg	36.0 %	Not reported	
Lettieri et al. 2006 [13]	79	Lung transplant and IPF referral center; Retrospective	mPAP>25 mmHg	31.6 %	Not reported	Linear correlation between mPAP and mortality
Hamada et al. 2007 [5]	70	University Hospital; Initial evaluation	mPAP>25 mmHg	8.1 %	Not reported	Worsened outcomes with mPAP>17 mmHg
Nathan et al. 2007 [14]	118	Retrospective review at referral center	mPAP>25 mmHg	40.7 %	Not reported	
Shorr et al. 2007 [16]	2,525	Lung transplant registry	mPAP>25 mmHg; Severe PH=mPAP >40 mmHg	46.1 %	9.0 %	Need for O_2, age, ethnicity, FEV1, PCO_2, PCWP associated with severe PH
Daniels et al. 2008 [15]	42	Autopsy data	Autopsy evidence of PH	45.0 %	Not reported	
Nathan et al. 2008 [17]	110	Retrospective review at two referral centers	mPAP>25 mmHg	34.5 %	Not reported	Study designed to assess TTE vs RHC for PH determination
Nathan et al. 2008 [18]	44	Comparison of RHC data from time of transplant to initial evaluation	mPAP>25 mmHg	86.4 %	Not reported	38.6 % at initial evaluation; Increased to 86.4 % by time of transplant
Todd et al. 2010 [19]	41	Retrospective review at referral center of ILD patients; IPF data extracted	mPAP>25 mmHg	29.3 %	Not reported	
Modrykamien et al. 2010 [20]	58	Retrospective review of transplanted patients at referral center	mPAP>25 mmHg and PCWP<15 mmHg	43.0 %	Not reported	
Boutou et al. 2011 [21]	81	Retrospective analysis of referral center data	sPAP>35 mmHg by TTE	57.0 %	Not reported	Resting sPAP correlated with impaired exercise capacity
Papakosta, et al. 2011 [22]	139	Prospective analysis at eight referral centers	sPAP>36 mmHg by TTE	55.0 %	Not reported	
Anderson et al. 2012 [23]	49	Prospective analysis of ILD patients; IPF data extracted	TTE screen; RHC if TTE suggestive; mPAP>25 mmHg; severe PH=mPAP>35 mmHg	24.5 %	14.2 %	May underestimate prevalence as only TTE+referred for RHC

Not all studies designed specifically to assess PH prevalence

CXR Chest radiography; *ILD* Interstitial lung disease; *IPF* Idiopathic pulmonary fibrosis; *mPAP* mean pulmonary artery pressure; *PCWP* Pulmonary capillary wedge pressure; *PH* pulmonary hypertension; *sPAP* systolic pulmonary artery pressure; *RHC* right heart catheterization; *TTE* Transthoracic echo; *UNOS* United Network for Organ Sharing

PASP of<35 mmHg, 36–50 mmHg, and>50 mmHg, respectively [11]. A similar study by Song and colleagues found one year mortality rates of 61.2 % for patients with PASP>40 mmHg vs. 19.9 % in those with PASP<40 mmHg [32].

Another IPF phenotype is combined IPF/emphysema. It is controversial as to whether these patients have worse or better outcomes than IPF patients without emphysema; however, what is well established is that this particular phenotype does have a greater propensity for PH. This makes sense from the standpoint that both pathologically distinct processes have the destruction of the pulmonary vasculature in common [33]. The importance of acute exacerbations of IPF (AE-IPF) on mortality has been recognized in recent years. A report by Judge et al. found PH to be a

significant risk factor for AE-IPF (HR=2.217, p=0.041) [34]. This association is possibly partially responsible for the adverse outcomes seen with IPF-associated PH.

Pathophysiology of pulmonary hypertension in IPF

PH in IPF was long thought to be due to the effects of hypoxic vasoconstriction and pulmonary capillary loss due to progressive fibrosis [35]. Hypoxic vasoconstriction leads to changes in vessel walls, including medial and intimal hypertrophy [36]. While hypoxic vasoconstriction almost certainly plays a role in PH in IPF, it cannot be the sole mechanism, as PH may develop in patients without hypoxemia [37]. Progressive destruction of the pulmonary vascular bed likely also contributes to the development of PH. Fibrosis in IPF is a heterogeneous process. In fibrotic areas, thickening of arterial and venous walls and severe luminal narrowing occurs, leading to increased pulmonary vascular resistance [38]. If progressive fibrosis were the primary mechanism leading to the development of PH in IPF, one would expect a correlation between the degree of restriction on pulmonary function testing and the development of PH. This relationship has not borne out, implying that other mechanisms contribute to pulmonary vascular disease in IPF [3].

If these two mechanisms alone fail to explain the pathogenesis of PH in IPF, then what mechanisms are responsible? Although incompletely understood, a complex interplay of multiple factors appears to be at work. A disruption in the balance of angiogenesis occurs, due to decreases in angiogenic factors such as vascular endothelial growth factor (VEGF) and an elevation of angiostatic factors including pigment-endothelium derived factor (PEDF). This may lead to decreased vascularity in fibrotic areas and hypervascularity in adjacent nonfibrotic areas. This leads to a net decrease in overall vessel density in the IPF lung [3]. Fibrotic regions may have both apoptotic and proliferating endothelial cells, resulting in anastomoses between alveolar capillaries and pulmonary veins [35]. Additionally, vessels in fibrotic regions may lack an elastin layer, reducing their capacitance and further contributing to PH [39].

A number of mediators responsible for the pathogenesis of fibrosis in IPF have been implicated in the development of PH as well. Profibrogenic leukotrienes, increased production of tumor necrosis factor α (TNF-α), platelet-derived growth factor (PDGF) and fibroblast growth factor, may all be involved in the development of both pulmonary vascular remodeling and fibrogenesis [40]. Endothelin-1 (ET-1) is both a potent vasoconstrictor and stimulator of smooth muscle cell proliferation [3]. These factors offer the potential for a therapeutic target that modifies both the fibrogenic and pulmonary vascular disease aspects of IPF. Unfortunately, the antifibrotic effects of endothelin antagonists have not been borne out in two recent large, prospective studies [41, 42].

Diagnosis

The diagnosis of pulmonary hypertension in the setting of IPF can be difficult. However, there is a growing interest in the evaluation for PH in IPF patients, given the important prognostic information imparted and the opportunity to rule out other contributory and modifiable factors, such as diastolic dysfunction. Additionally, there is ongoing interest in the diagnosis of "out of proportion PH," since this might be the specific sub-phenotype most amenable to trials of vasoactive therapies.

Signs and symptoms of PH in IPF patients are nonspecific and may be subtle, since the PH is often mild. Physical exam findings such as a tricuspid regurgitant murmur, a loud pulmonary component of the second heart sound, or a RV heave, are unusual and therefore are not sufficiently sensitive to diagnose PH. Likewise, EKG may show signs of right heart strain, but this finding also lacks sensitivity and specificity for predicting PH.

RHC with direct measurement of pressures has been the gold standard for the diagnosis. However the invasive nature of this procedure is not ideal for routine assessment and serial follow-up to assess therapeutic response. Thus, there has been great interest in the development of a noninvasive measure to diagnose pulmonary hypertension. Past efforts focused on the use of spirometry, the single breath diffusing capacity for carbon monoxide (DL_{CO}) and 6MWT, to predict the presence of PH. Multiple investigators have demonstrated that spirometric values do not distinguish which IPF patients have PH [14]. However, the DL_{CO} may have some value in this regard, especially once it decreases to<40 % of predicted. The use of noninvasive indicators in parallel can improve the performance characteristics and accuracy for predicting PH. For example, the combination of DL_{CO}<40 % predicted and resting room air saturation<88 % has been shown to be predictive of PH, with positive and negative predictive value of 87 % and 82 %, respectively [13].

Given the failure of spirometry and limitations of the DL_{CO} to predict PH, efforts have focused on the use of exercise parameters, biomarkers and radiological studies to predict IPF-related PH. Patients with early PH may have normal resting PA pressures but develop elevated pressures with exertion. Several exercise parameters may be useful in suggesting PH in patients with IPF. Multiple investigators have demonstrated that desaturation on 6MWT is associated with PH. As previously noted, in the Lettieri study, IPF patients with PH had a lower oxygen saturation nadir (80.1±3.7 % vs. 88.0±3.5 %, p<0.001) and decreased distance walked (143.5±65.5 m vs. 365.9±81.8 m, p<0.001) on 6MWT [13]. In another series, desaturation to<85 % on 6MWT was 100 % sensitive for PH, but not specific [17]. Other investigators have demonstrated that more severe exercise limitation is associated with higher pulmonary pressures

by echocardiography [21, 43]. Therefore, desaturation greater than expected, or severe limitation on exercise testing should prompt consideration of PH. Another exercise parameter that has been used to evaluate for PH is the heart rate recovery (HRR), defined as the difference between the heart rate at the end of the 6MWT and after one minute of recovery. Recently, Swigris et.al found that a HRR<13 beats/minute had negative and positive predictive values of 82 % and 41 %, respectively, for pulmonary hypertension, and also predicted increased mortality [44].

Serum brain natriuretic peptide (BNP) levels are elevated in PH, and are strongly correlated with increased mortality in interstitial lung disease [45]. Leuchte et al. showed that in patients with lung fibrosis, those with elevated levels had significantly higher PAP on RHC than those with normal BNP levels (mPAP 40.9 mmHg vs. 23.4 mmHg) [46]. The specific role of BNP levels in the diagnosis of PH remains to be defined.

CT has also been used to evaluate for pulmonary hypertension. In a general population, increased pulmonary artery size as indicated by the ratio of the diameter of the main pulmonary artery to aortic diameter>1 has been shown to be an indicator of PH [47]. However, in patients with IPF, no CT findings, including mean pulmonary artery diameter and ratio of pulmonary artery to aortic diameter, were able to differentiate between those with and without PH [48]. It has been suggested that a cutoff of 29 mm for the mean pulmonary artery diameter has reasonable negative predictive value, albeit poor positive predictive value for the presence of PH, implying that IPF patients with measurements below this value may not require further evaluation with RHC [49, 50]. In summary, the cumulative data suggests that the performance characteristics of the PA size as a predictor of PH lacks sufficient accuracy to be solely relied upon.

Estimation of pulmonary artery systolic pressure (PASP) by echocardiographic assessment of the tricuspid regurgitant jet has long been used as a widely available and noninvasive surrogate for RHC measurement of pulmonary pressures. However, the TR jet may be absent or not visualized. Additionally, obtained values may both overestimate and underestimate values for PASP compared to the gold standard right heart catheterization. In patients with advanced lung disease, including those with IPF, the PASP can only be estimated in approximately half of patients, and in those cases where it is estimated, approximately half of patients may be misclassified as having PH [17, 24]. These data indicate that although echocardiography may be a useful part of an overall assessment for PH, it does not replace RHC for the definitive diagnosis. Use of noninvasive tests in combination has appeal in order to improve the overall accuracy of predicting PH. For example, it has recently been shown that a combination of CT findings and echocardiographic findings together was more predictive of PH by RHC than either study alone [51]. Future efforts should concentrate on identifying which combinations of tests best identifies or excludes PH and most closely correlates with right heart catheterization data. At this time however, RHC remains the gold standard for the diagnosis of PH in all patient groups.

Treatment

Therapy for patients with PH-IPF can be divided into conservative, or non-pharmacologic interventions, and vasoactive medications. Non-pharmacologic interventions include addressing comorbidities such as resting hypoxia, sleep-disordered breathing, as well as cardiovascular and thromboembolic disease. Long-term oxygen therapy (LTOT) is widely accepted as empiric therapy for patients with IPF when the PaO2<60 mmHg, with a goal to maintain the SpO2>90 %. There is no evidence that LTOT improves survival or pulmonary hemodynamics in IPF [52]. Similarly, supplemental oxygen has not been shown to prevent increases in mPAP during exercise in this population [7]. However, limited data support a potential benefit in improving exercise capacity [53, 54], and current guidelines recommend the use of LTOT in PH-IPF in the setting of resting hypoxemia [55].

An assessment for and the treatment of sleep-disordered breathing is prudent, given the ability to effectively diagnose obstructive sleep apnea (OSA) with nocturnal polysomnography, and the potential for CPAP therapy to improve nocturnal desaturations and quality of life. OSA has a high prevalence in patients with IPF (88 %) [56], and both sleep apnea and chronic nocturnal hypoxia can potentially lead to or perpetuate PH.

At the present time, there is limited data regarding the safety and efficacy of vasoactive therapies for PH-IPF. Vasodilators have demonstrated benefits for certain clinical endpoints such as exercise and functional capacity, but not survival (Table 2) [42, 57–66, 67•, 68, 69]. Vasodilators have the potential to worsen hypoxemia in IPF by inhibiting hypoxic vasoconstriction in regions with low ventilation to perfusion ratios [57, 60, 70]. Additionally, the existence of pulmonary veno-occlusive disease (PVOD)-type lesions have been described in up to two-thirds of patients with IPF, and may be associated with acute pulmonary edema with the use of vasodilator therapy [38, 71–73]. Current guidelines recommend against the routine use of vasodilator agents in patients with PH-IPF, with the caveat that these agents may be considered in specific subgroups of patients, such as those with severe PH (mPAP>35 mmHg) [55]. This is best done in the setting of a clinical trial or an experienced center.

Three small studies ($n \leq 10$ patients each) have demonstrated that inhaled nitric oxide (iNO) is selective for pulmonary vasodilation, preserves gas exchange and reduces

Table 2 Trials of therapy for pulmonary hypertension in advanced ILD and IPF

Author	Type of Study	*N*	Therapy	Outcome
Yoshida et al. 1997 [66]	Case series	10	iNO and iO_2	Positive study: Reduced PVR and mPAP, with ↑in PaO2 in 5/10 patients
Olschewski et al. 1999 [57]	Prospective cohort	8	IV prostacyclin, iNO, aerosolized prostacyclin, iO_2, CCB	Equivocal study: Aerosolized prostacyclin (iloprost) caused marked pulmonary vasodilation with maintenance of gas exchange and systemic arterial pressure; intravenous prostacyclin increased shunt flow and was not selective for pulmonary vasculature
Ghofrani et al. 2002 [60]	RCT, open-label	16	Sildenafil	Positive study: Improved gas exchange and selective pulmonary vasodilation
Madden et al. 2006 [69]	Prospective cohort	7 (mixed study population, 3 patients with IPF)	Sildenafil	Positive study: Reduction in PVR, est PAP, CO/CI, and increased 6MWT and subjective well being; drug well tolerated
Madden et al. 2007 [64]	Prospective cohort	16 (mixed study population, 2 patients with IPF)	Sildenafil	Positive study: Significant reduction in mPAP, 6MWT, and well tolerated
Gunther et al. 2007 [61]	Prospective cohort	12	Bosentan	Positive study: No worsening of gas exchange
Collard et al. 2007 [59]	Open label prospective trial	11	Sildenafil	Positive study: 57 % had an increase in 6MWT distance of≈50 meters
King et al. 2008 [63]	RCT, double-blind	158	Bosentan	Negative study: No improvement in primary outcome measure of 6MWT distance, but trends toward improvements in QOL and delayed progression of disease or delay in death
Minai et al. 2008 [65]	Retrospective case series	19	IV epoprostenol and bosentan	Equivocal study: Initial, but non-sustained, functional benefit and improved 6MWT distance
Zisman et al. 2010 [67•]	RCT, double-blind	180	Sildenafil	Negative study: Primary outcome of increased 6MWT distance not met; small but significant improvements in secondary outcome measures
Jackson et al. 2010 [62]	RCT, double-blind	29	Sildenafil	Negative study: No difference in 6MWT or Borg score
King et al. 2011 [42]	RCT, double-blind	616	Bosentan	Negative study: Primary outcome of delay in IPF progression or delay of death not met; no impact on other secondary outcomes such as quality of life or dyspnea; medication well tolerated
Blanco et al. 2011 [68]	Case series	7	iNO	Positive study: iNO significantly decreased PVR both at rest and during exercise without worsening oxygenation

IPF idiopathic pulmonary fibrosis, *RCT* randomized clinical trial, *6MWT* 6-minute walk test, *NYHA/WHO* New York Heart Association and World Health Organization, *IV* intravenous, *iNO* inhaled nitric oxide, iO_2 inhaled oxygen, *CCB* calcium channel blockers, *PASP* pulmonary artery systolic pressure, *TTE* transthoracic echocardiography, *CI* cardiac index, *CO* cardiac output, *RHC* right heart catheterization, *mPAP* mean pulmonary artery pressure, *PVR* pulmonary vascular resistance, *ILD* interstitial lung disease

pulmonary vascular resistance (PVR) [57, 66, 68]. There is no literature on clinical outcomes, as iNO is currently unavailable on a long-term ambulatory basis.

Several smaller studies on sildenafil have yielded conflicting outcomes [59, 60, 62, 64, 69]. A placebo-controlled trial of sildenafil was performed in 180 patients with IPF to evaluate the impact on exercise performance (6-minute walk) [67•]. Although this study failed to demonstrate an improvement in the primary endpoint, there were significant improvements in secondary endpoints including dyspnea, and quality of life, as well as a trend towards a survival benefit. While this study was limited by a lack of RHC data, it likely included a significant number of patients with PH-IPF given the main inclusion criteria of DLco<35 %. A pre-specified post-hoc analysis of those with TTE-evidence of PH demonstrated a significant improvement in the primary endpoint [74].

The dual endothelin receptor antagonist bosentan appears to be safe in IPF [42, 61, 63, 65]; however, efficacy appears to be limited. In a phase 3 study (BUILD-1) [63] evaluating its antifibrotic properties, no significant benefit was demonstrated in improving the primary endpoint of 6-minute walk distance. There were trends towards improvements in secondary endpoints, including delayed disease progression, time to death and quality of life. Subgroups analysis of the

patients in this study with PH was not possible due to limitations of the study design. However, a follow-up study (BUILD-3) [42] performed to evaluate the endpoint of delayed disease progression and time to death, failed to find any significant differences. Ambrisentan has been studied in patients with PH-IPF (Artemis-PH study [41]); however, this study was terminated early due to potential harm in IPF patients in the parallel Artemis-IPF study. The inhaled prostacyclin iloprost has been studied in patients with echocardiographic evidence of PH, but also with negative results [58]. Preliminary studies on the oral dual endothelin receptor antagonist macitentan in patients with IPF also found this endothelin antagonist to be of no discernible benefit [75, 76].

Further studies of currently available and future PH drugs are strongly encouraged to better define the phenotype of patients (if any) most likely to respond to this therapeutic strategy. A search of http://clinicaltrials.gov (June 14th, 2012) yielded few active studies looking specifically at PH-IPF ("idiopathic pulmonary fibrosis," "pulmonary hypertension," "pulmonary hypertension and IPF," and "pulmonary hypertension and pulmonary fibrosis"). Pending the availability of such studies, if off-label PH therapy is to be considered in IPF, it should be done with patients fully informed of the potential effects, both helpful and harmful, and with their full consent and close serial monitoring. This is best achieved in the context of Tertiary Care referral Centers with experience in both IPF and PH.

Lung transplantation is presently the only therapy that confers a survival advantage [77]. Given the lack of other effective therapies, and the progressive nature of this disease, IPF is a leading indication for transplant [78, 79]. The 5-year survival varies between 44–56 % [55, 78, 80–83], and transplant should therefore be regarded as more of a palliative procedure, rather than a cure. It is controversial as to whether single lung transplants (SLT) or bilateral lung transplants (BLT)) are the optimal procedure for patients with IPF. Any potential advantage of BLT should be weighed against the risk of longer wait times and the inherent risk of dying on the transplant list [84]. Barriers that limit the timeliness of transplant include delays in the diagnosis and referral to a transplant center, as well as the availability of donor organs [85].

Future directions

Gene microarray technology has been used to identify unique genetic signatures in lung tissue. Gene expression profiles from patients with idiopathic pulmonary arterial hypertension (IPAH) and secondary PH (such as PH-IPF) have the potential to help better define individual risk factors for pulmonary vascular disease, disease progression, and response to therapy [86].

Rajkumar and colleagues [87] evaluated genes involved in the pathogenesis of PH and generated a molecular signature of 4,734 genes that discriminated between patients with IPAH, PH-IPF, and normals. Tissue specimens were taken from patients undergoing lung and heart-lung transplantation. Numerous signaling pathways were implicated in the pathophysiology of PH, and the genetic signatures and resultant biologic pathways differed between IPAH and PH-IPF.

A recent study by Mura et al. [88••] further delineated the differences between IPF patients with and without associated PH, using microarray analysis of lung specimens. This study identified a genetic signature of 222 differentially expressed genes distinguishing IPF patients with and without PH. Patients were grouped based on right heart catheterization (*Severe PH*: mPAP≥40 mmHg, *Intermediate PH*: 21–29 mmHg, *No PH*: ≤ 20 mmHg), and were well matched with regards to demographic and clinical characteristics, with the exception of DL_{CO}. Those with *Severe PH* had increased expression of genes related to extracellular matrix remodeling, fibroblast migration, and pulmonary artery smooth muscle cell proliferation and migration. The genetic signature of PH-IPF appears to be pro-proliferative, with PH driven by aberrant proliferation of fibroblasts and pulmonary artery smooth muscle cells. By contrast, genes upregulated in the *No PH* group consisted primarily of proinflammatory cytokines and cytokine receptors.

Studies on genetic signatures of PH and IPF improve our understanding of the complex pathophysiology and interplay of both. In the future, genomic fingerprinting may assist in identifying the pathways implicated in the pathophysiology of IPF and PH, and enable a pharmacogenetic approach to therapy. Gene expression profiling of either lung specimens or peripheral blood cells may also find utility as biomarkers of disease, and to screen at-risk populations for IPF or established IPF patients for their propensity to develop complicating PH. Ultimately, correlating the effectiveness of a therapy with unique genetic signatures could improve efforts to prevent disease progression in IPF-PH.

Conclusion

PH has a high prevalence among patients with IPF and independently worsens outcomes. While noninvasive strategies are valuable for screening and risk stratification, only RHC is appropriate to establish the diagnosis. Supplemental oxygen and treatment of other comorbidities should be part of any comprehensive treatment strategy. Randomized controlled studies of pulmonary vasoactive agents have mostly been negative to date, but there remains suggestive evidence that such a targeted approach might be of use in appropriate patients [67•]. Genetic profiling may be the ultimate tool that best identifies such patients and may hold the key to future individualized targeted therapies in both PH and IPF, as well as PH complicating the course of IPF.

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