REGULAR ARTICLE

Management of PH-ILD: Past, Present, and Future

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Pulmonary hypertension associated with interstitial lung disease signifies worse outcomes. Given previous negative clinical trials, the use of pulmonary vasodilators in pulmonary hypertension associated with interstitial lung disease has traditionally been on a case-by-case basis; however, the recent INCREASE study has led to the first and milestone approval of inhaled treprostinil for this population. This review discusses the management of pulmonary hypertension associated with interstitial lung disease from the pulmonary vascular perspective, with an emphasis on clinical trials in this population.

INTRODUCTION

Pulmonary hypertension (PH) in interstitial lung disease (ILD) is a serious complication that heralds significant morbidity and mortality.[1,2] Apart from early referral for transplantation evaluation, management of PH associated with ILD (PH-ILD) focuses on treatment of the individual parenchymal and pulmonary vascular disorders. While the advent of multiple therapeutics for pulmonary arterial hypertension (PAH) has sparked much interest in their use in PH-ILD, the first Food and Drug Administration approval for such a medication was granted only recently. This review will focus on the management of PH-ILD, with particular reference to previous and current pharmacologic studies in this area.

CHALLENGES TO CLINICAL TRIALS

Clinical trials in PH-ILD have faced multiple unique challenges stemming from the complexity inherent in diagnosing and managing a combined cardiopulmonary disorder. Potential disruption of ventilation-perfusion matching led to the exclusion of this population from the original medication trials; instead, initial work largely consisted of small series in PH-ILD and subgroup analyses of ILD-only studies. From a diagnostic perspective, conclusions from these studies are limited: not only were many based on echocardiography, but those with invasive hemodynamics generally did not include the pulmonary vascular resistance (PVR), a now-required component of the 6th World Symposium on Pulmonary Hypertension (WSPH) definition of Group 3 disease.[2] Similar variations in the studied lung disease subtype and severity have also limited comparison between analyses.

Clinically, PH-ILD exists on a spectrum, and it may be difficult to untangle the contribution of each disease to symptom burden and functional limitation. From a trial perspective, this has created considerable difficulty in determining the most appropriate endpoint in PH-ILD: ideally, such a metric would accurately delineate parenchymal and pulmonary vascular limitations, reproducibly monitor treatment response, and carry prognostic significance. The 6-minute walk distance (6MWD)—the standard exercise assessment in PAH—is often used in PH-ILD; however, it is affected by each individual disease and cannot distinguish between them.[3] Going forward, composite endpoints that include separate PH-specific and ILD-specific parameters and overall functional measures will likely be helpful. Similarly, cardiopulmonary exercise testing to differentiate limitations or cardiac magnetic resonance imaging to evaluate right ventricular (RV) function may also be important tools.[3]

THE NITRIC OXIDE PATHWAY

Phosphodiesterase-5 Inhibitors

The earliest studies of PAH-specific therapy in PH-ILD focused on phosphodiesterase-5 inhibitors. Initial small studies noted phosphodiesterase-5 inhibitors positively impacted hemodynamics and exercise capacity in PH-ILD.[4-6] Compared to intravenous epoprostenol, sildenafil also enhanced ventilation-perfusion matching—at least partly because of reduced shunting—and ultimately improved oxygenation.[7] This phenomenon was attributed to preferential vasodilation of well-ventilated regions of lung, potentially from the effect of sildenafil on local vasoregulation including nitric oxide.[7]

The Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) study was a double-blind randomized controlled trial (RCT) of sildenafil in advanced idiopathic pulmonary fibrosis (IPF), defined by a diffusing capacity for carbon monoxide (DLCO) <35%. There were small improvements in oxygenation, DLCO, dyspnea, and quality of life with sildenafil, although it was not associated with increased 6MWD.[8] While patients on background PAH therapy were excluded, a small number (18.6%) had RV

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hypertrophy or dysfunction on echocardiogram. While the entire population experienced a decrease in 6MWD, this finding was attenuated among patients with RV dysfunction treated with sildenafil.[9]

Based on these positive results, it was hypothesized that phosphodiesterase-5 inhibitors and antifibrotics may work synergistically in PH-IPF. INSTAGE, a double-blind RCT, evaluated the combination of sildenafil and nintedanib, a tyrosine kinase inhibitor with antifibrotic properties, in IPF with severely impaired gas exchange (DLCO ≤ 35%).[10] Compared to nintedanib alone, quality of life was not improved with nintedanib-plus-sildenafil. Among the subgroup with echocardiographic RV dysfunction (43%), there was a more pronounced stabilization of BNP—likely reflecting reduced RV stress—although this again did not translate to improved quality of life.[11]

Similar equivocal results were recently reported from a Phase 2b RCT of sildenafil and pirfenidone, an antifibrotic that blocks the proliferative effects of platelet-derived growth factor, in advanced IPF with DLCO ≤ 40%. Notably, this study enrolled only patients at risk of WSPH Group 3 disease, defined either by PH on right heart catheterization (mean pulmonary arterial pressure ≥20 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg) or intermediate-high probability on echocardiogram.[12] Pirfenidone-plus-sildenafil was not associated with a change in disease progression, exercise capacity, quality of life, or pulmonary function. The addition of sildenafil to antifibrotics is therefore not routinely recommended in IPF, although certain subpopulations may benefit from this treatment approach.

Riociguat

Initial open-label evaluation of the soluble guanylate cyclase stimulator riociguat in treatment-naive PH-ILD patients suggested it was both safe and well-tolerated.[13] RISE-IIP (Riociguat for Idiopathic Interstitial Pneumonia-Associated PH) was a subsequent RCT studying riociguat in PH associated with idiopathic interstitial pneumonias (IIPs) with forced vital capacity (FVC) ≥45%.[14] RISE-IIP was terminated early at 22 weeks: not only did riociguat fail to improve exercise capacity, but treated patients also had increased rates of adverse events including deaths. The reason for this clinical worsening is not clear but has been attributed to the wide variety of enrolled ILDs with different long-term prognoses or the possibility of a harmful hemodynamic response causing increased RV workload.[13] Regardless, the use of riociguat is not recommended in PH-IIP.

THE ENDOTHELIN-1 PATHWAY

While initially thought promising due to additional parenchymal antifibrotic effects, studies of the endothelin receptor antagonists have been largely underwhelming. Although an early case series suggested the dual endothelin receptor antagonist bosentan increased exercise capacity in PH-ILD, this finding did not persist at 1 year.[15] Negative results were also seen in B-PHIT, a placebo-controlled RCT of bosentan in fibrotic PH-IIP. Among 60 patients, this medication was not associated with improvements in indexed PVR, exercise capacity, dyspnea, or oxygenation.[16] In contrast, interim results from a small open-label study suggested bosentan improved hemodynamics and survival in patients with exercise or mild-moderate PH and IPF without parenchymal inflammation.[17] As the inclusion of only stable lung disease minimized confounding from respiratory exacerbations, it was suggested this may more accurately reflect the effect of bosentan on the pulmonary vasculature.

While studies of bosentan were mixed, evaluation of the selective endothelin receptor antagonist ambrisentan in PH-ILD has been disappointing. Within the small PH-ILD population (9.4%) in the open-label ARIES-3 study, 6MWD decreased at 24 weeks despite improved BNP, potentially related to progressive underlying lung disease.[18] The double-blind ARTEMIS-IPF RCT was subsequently initiated to evaluate ambrisentan in IPF with no-to-minimal honeycombing; however, it was terminated early at 75% enrollment because of poor efficacy and increased adverse events.[19] While those on background PAH treatment were excluded, 14% of the original cohort had WSPH Group 3 disease on preenrollment right heart catheterization.[20] After 48 weeks of randomized treatment, ambrisentan was not associated with hemodynamic improvements among those who underwent interval right heart catheterization. Moreover, there was a nonsignificant trend among ambrisentan-treated PH patients toward increased ILD progression. Endothelin receptor antagonists are therefore not routinely recommended for treatment of PH-ILD.

THE PROSTACYCLIN PATHWAY

Intravenous Prostacyclins

The most favorable results in PH-ILD treatment have centered on prostacyclins. In an early comparison study, inhaled iloprost was associated with decreased mean pulmonary arterial pressure and PVR, without adverse impact on oxygenation.[21] Hemodynamic improvements were largely similar with intravenous epoprostenol, although they occurred at the expense of systemic vasodilation. The use of parenteral treprostinil therapy in 15 patients awaiting lung transplantation with severe pulmonary fibrosis-associated PH was similarly promising. While most patients were on background PAH therapy—such that the study was enriched for a population that had already tolerated pulmonary vasodilators—hemodynamics significantly improved at 12 weeks, which correlated with better RV function on both echocardiographic and invasive assessment.[22] Exercise capacity, dyspnea, and quality of life also improved with stable oxygenation. Similar hemodynamic improvements have also been noted with parenteral treprostinil in an autoimmune disease-containing PH-ILD population.[23]

Inhaled Prostacyclins

Inhaled treprostinil is currently the most effective treatment for PH-ILD, leading to its recent approval by the Food and Drug Administration as the first therapeutic option for this population. In an initial retrospective review of 22 WSPH Group 3 PH patients—the majority of whom had ILD or combined pulmonary fibrosis and emphysema—inhaled tre-

prostinil was associated with improved functional class, exercise capacity, and oxygenation.[24]

The recent double-blind placebo-controlled INCREASE study was the first RCT of inhaled treprostinil in PH-ILD.[25] Inclusion criteria necessitated PH on right heart catheterization—notably with an elevated PVR > 3 Wood units—and diffuse parenchymal lung disease on computed tomography chest scan. The study met its primary endpoint: at 16 weeks, there was a significant difference between the treprostinil-treated and placebo-treated cohorts in the change in peak 6MWD from baseline (least-squares mean difference 31.1 m, $P < .001$). Notably, the largest increases occurred in the subgroups with PVR ≥ 4 WU or DLCO < 40%, suggesting that patients with the most severe—and likely disproportionate—pulmonary vascular remodeling benefited the most from treatment.

Importantly, inhaled treprostinil treatment was also associated with improved markers of clinical status and RV function. Time to clinical worsening—a composite of 6MWD decline, cardiopulmonary hospitalization, lung transplantation, and all-cause mortality—was significantly prolonged with treatment. NT-proBNP decreased with inhaled treprostinil but rose precipitously with placebo, without change in oxygenation. These results therefore suggest inhaled treprostinil ameliorated RV stress, likely through improved perfusion of only well-ventilated lung and preservation of ventilation-perfusion matching.

Interestingly, INCREASE revealed a number of unexpected findings with potential significance in ILD. Inhaled treprostinil was associated with a significantly reduced rate of ILD exacerbations. Furthermore, FVC rose with treatment (inhaled treprostinil vs placebo, absolute difference 44.4 mL [$P = .21$]; predicted change 1.8% [$P = .028$]).[26-28] Notably, this finding occurred despite the wide range of studied ILDs—including combined pulmonary fibrosis and emphysema—and was driven by a true FVC increase, not between-group rates of decline as observed in previous antifibrotic trials. This improvement was most prominent among the IPF subgroup, as well as those with increased pulmonary vascular remodeling and likely RV stress (PVR ≥ 5.275 WU; NT-proBNP >503.85 pg/mL). While the physiologic mechanism underpinning these findings is not yet clear, it may be related to antifibrotic effects of inhaled treprostinil, potential impact of pulmonary vascular stiffness on parenchymal compliance, or possible interactions between RV stress and respiratory muscle function.[26,29,30] A double-blind RCT studying the pulmonary effects of inhaled treprostinil in IPF is currently ongoing (ClinicalTrials.gov identifier NCT04708782).

NONPHARMACOLOGIC MANAGEMENT

General Principles

Study of the nonpharmacologic care of PH-ILD is limited. Screening with management of related comorbidities is encouraged, as are lifestyle modifications including smoking cessation. As oxygen in ILD is not a well-studied therapy, recommendations derive largely from chronic obstructive pulmonary disease, where long-term oxygen therapy (≥15 h daily) is recommended in severe hypoxemia (defined as (1) partial pressure of oxygen ≤55 mm Hg or oxygen saturation ≤88%, or (2) partial pressure of oxygen = 56 mm Hg to 59 mm Hg or oxygen saturation = 89% plus one of edema, hematocrit ≥55%, or P pulmonale on electrocardiogram).[31,32] While recent guidelines suggest application of the same criteria for long-term oxygen therapy in ILD, there are no recommendations for PH-ILD.[32] Until official guidelines are established, frequent evaluation for hypoxemia—with treatment when it is severe—is generally advised.[2]

Transplantation

Lung transplantation is an important management option in PH-ILD. Guidelines recommend referral for evaluation in ILD including for any patient with IPF, fibrotic nonspecific interstitial pneumonia, FVC <80%, DLCO < 40%, oxygen requirement, dyspnea, or functional limitation.[33] Furthermore, listing is recommended for any eligible patient with concurrent PH.[33] As the wait time may be extensive, artificial support may be employed as a *bridge* to transplantation in a select population.[2,33]

FUTURE DIRECTIONS

There is growing interest in the use of novel therapeutics in PH-ILD. Pulsed inhaled nitric oxide was associated with improved moderate-vigorous physical activity and oxygenation in a phase 2b trial in fibrotic PH-ILD, and a phase 3 trial is currently enrolling (Clinical Trials.gov identifier NCT03267108).[34] Furthermore, as efforts to better phenotype and understand PH-ILD continue through programs like PVODMICs, this will hopefully provide a future basis for the clearer delineation of study populations and endpoints reflective of individual disease burden.

CONCLUSIONS

The development of PH in ILD portends a poor prognosis. Given the many negative clinical trials, PAH-targeted medications have historically been used on a case-by-case basis. The recent INCREASE trial of inhaled treprostinil represents a milestone in PH-ILD, such that this is the first medication approved by the Food and Drug Administration for treatment of this group. As understanding of PH-ILD grows, this will hopefully drive the emergence of novel agents, selection of specific trial populations, and definition of accurate endpoints to promote additional therapeutic options for this cohort.

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