Future Therapies in PAH: Update on the New Landscape and Drugs in the Pipeline

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Research in pulmonary hypertension (PH) in general and in pulmonary arterial hypertension (PAH) in particular has been extremely active in the past few years. The current therapeutic landscape includes multiple compounds shown to be active in modulating and ameliorating the pathological changes in the endothelin, nitric oxide (NO), and prostacyclin pathways. In addition, development of new compounds targeting pathways of pulmonary vascular remodeling due to inflammation, fibrosis, and oxidative stress is underway. This review summarizes the most recent achievements and newly conducted clinical trials—some with novel trial design—for treatment of PH and PAH.

ADDRESSING ESTABLISHED SIGNALING PATHWAYS

A Novel Endothelin Receptor Antagonist: Macitentan

Until recently, 2 endothelin receptor antagonists (ERAs), bosentan and ambrisentan, have been available for the treatment of pulmonary arterial hypertension (PAH). Macitentan is a novel dual ERA with a long half-life, potent inhibition profile of endothelin receptors, and strong lipophilic profile, suggesting stronger affinity for tissue.[1] The efficacy of oral macitentan was evaluated in the randomized, double-blind, multicenter, placebo-controlled, event-driven SERAPHIN study (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome), which is the largest of its kind published thus far.[2] SERAPHIN is the first event-driven trial in PAH that uses a composite primary endpoint: the time from initiation of therapy to the occurrence of the first PAH-related event (ie, worsening of PAH, initiation of treatment with intravenous [IV] or subcutaneous [SC] prostanoids, lung transplantation or atrial septostomy, or death from any cause up to the end of treatment). Treatment with macitentan 10 mg once daily significantly reduced the risk for the primary composite endpoint by 45% ($P<0.001$) in patients with PAH (mostly World Health Organization [WHO] functional class II or III), with the treatment effect largely attributable to a reduction in clinical worsening events. Other efficacy outcomes, including exercise capacity, hemodynamic parameters, and health-related quality of life also improved significantly with macitentan relative to placebo. Macitentan was generally well tolerated in this study. As with other ERAs, hemoglobin levels may decrease with macitentan; however, this effect occurred early, was not progressive, and stabilized following long-term treatment. As a result of the SERAPHIN study, the Food and Drug Administration (FDA) recently approved macitentan for treatment of PAH.

Novel Means to Address the Prostacyclin Pathway: Selexipag, Oral Treprostinil, and New Delivery Systems

Given the cumbersome administration of parenteral prostacyclins and the limitations of inhaled therapies, oral prostacyclin analogues as well as new delivery systems of current parenteral prostacyclin analogues are being tested to improve ease of administration.

Selexipag is a derivative of 4,5-diphenyloxazole, an oral pro-drug that is hydrolyzed to the active metabolite, a selective, high affinity prostacyclin receptor agonist. In a Phase 2 study, Simonneau et al[3] reported data on 43 symptomatic PAH patients treated with an ERA and/or phosphodiesterase 5 (PDE5) inhibitor, randomized to active drug or placebo.[3] The dose was uptitrated from 200 μg twice a day to maximum 800 μg twice a day as tolerated. Primary outcome with significant decrease in pulmonary vascular resistance was achieved with good safety and tolerability profile. A large multicenter, placebo-controlled, double blind, event-driven study enrolling 1156 PAH patients on background ERA and/or PDE5 inhibitor was conducted, with the primary outcome of time to first clinical worsening.[4] The trial just concluded and the results are pending.

Treprostinil, a prostacyclin derivative, has been available as an IV or SC continuous infusion, or as inhaled therapy. Most recently, the oral formulation of treprostinil was studied in 3 multicenter, double blind, randomized, placebo-controlled trials. FREEDOM-C randomized 350 patients on background oral therapies (ERAs and/or PDE5 inhibitors).[5] Placebo-corrected median improvement in 6-minute walk distance (6MWD) was 11 meters ($P=0.07$), although there were significant improvements in dyspnea score and in the combined 6MWD and dyspnea score. Patients who achieved a Week 16 dose of 1.25 to 3.25 mg and 3.5 to 16 mg twice a day experienced a greater change in 6MWD than patients who achieved a

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dose of <1 mg or discontinued due to side effects, suggesting a dose-related efficacy. In the FREEDOM-C2 trial, 310 patients stable on ERAs and/or PDE5 inhibitors were randomized to receive placebo or active drug over 16 weeks.[6] Because at the initiation of drug uptitration the first dose was lower than in the initial FREEDOM–C trial, the drug was better tolerated. Nevertheless, the placebo-corrected median difference in 6MWD did not achieve statistical significance (10 meters, $P=0.089$), nor did secondary endpoints. Lastly, FREEDOM-M evaluated oral treprostinil as monotherapy for PAH.[7] Three hundred forty-nine patients were randomized to receive active drug or placebo over 12 weeks. There were significant improvements in the primary outcome, 6MWD, compared with placebo. In the intention to treat analysis, the improvement was 26 meters ($P=0.0001$) at peak and 17 meters ($P=0.0025$) at trough plasma study concentrations. Secondary endpoints did not achieve statistical significance. The side effects most commonly encountered in the 3 studies were headache, diarrhea, nausea, flushing, and jaw pain. As a result of the FREEDOM studies in correlation with the previously approved nonoral formulations of treprostinil, oral treprostinil became the first oral prostacyclin analogue approved by the FDA for the treatment of PAH. Oral treprostinil can be given 2 or 3 times a day and should be administered with food to minimize gastrointestinal side effects. The dose is titrated as tolerated to achieve improvement in symptoms and exercise capacity.

Novel delivery systems for IV prostacyclins are being investigated, with the goal to increase patient convenience and decrease the risk of catheter-related bloodstream infections. For this purpose, an implantable pump delivery system is being studied for IV treprostinil delivery. The purpose of the DellVery trial (Device Implantable Intravascular Catheter to deliver Remodulin in PAH) is to assess the safety of the Model 10642 implantable intravascular catheter used in combination with the SyncroMed II implantable infusion system to deliver treprostinil intravenously.[8] The study has enrolled 40 patients stable on IV treprostinil, and the primary endpoint is the rate of catheter-related complications per 1000 patient days. While the SyncroMed II has been approved for delivery of other therapies, such as cancer treatment, it has not been approved to deliver treprostinil. If proven safe, this mode of delivery will most likely improve the quality of life of PAH patients requiring parenteral treprostinil.

Novel Ways to Enhance the Cyclic Guanosine Monophosphate Pathway: Soluble Gualylate Cyclase Stimulators

Riociguat is a member of a new class of pharmacologic agents called soluble gualylate cyclase (sGC) stimulators, which aim to increase cyclic guanosine monophosphate (cGMP) availability.[9] Riociguat stimulates sGC in a nitric oxide (NO)-independent, heme-dependant manner, and it is also capable of synergizing with NO over a wide range of concentrations. By synergizing with NO, riociguat increases the sensitivity of sGC to NO.[9,10] On the other hand, the NO-independent action of riociguat distinguishes it from PDE5 inhibitors, which require NO to function and may have limited efficacy in the presence of very low NO levels.[11] Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (PATENT-1) investigated the efficacy and tolerability of riociguat in patients with symptomatic PAH who were either treatment-naïve, or pretreated with ERAs or prostanoids (excluding the IV forms). Riociguat significantly improved 6MWD and exercise capacity, and significantly and consistently improved secondary efficacy endpoints (pulmonary hemodynamics, functional class, and time to clinical worsening) and was well tolerated, with a favorable safety profile.[12] Thus, riociguat is a treatment option for PAH, either as a first-line or as an add-on therapy.

Novel Treatments for Chronic Thromboembolic Pulmonary Hypertension: sGC Stimulators and Balloon Pulmonary Angioplasty

Until recently, pharmacologic agents specifically targeting the pulmonary vasculature had only been approved for PAH (Group 1 as per World Symposium on Pulmonary Hypertension [PH] classification, Nice, France).[13] Nevertheless, PAH-targeted therapies have been commonly used in chronic thromboembolic pulmonary hypertension (CTEPH) patients (Group 4 as per World Symposium on PH classification, Nice, France), despite insufficient scientific evidence for their efficacy. A major milestone for patients with inoperable or persistent/recurrent CTEPH was achieved recently. The Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator trial-1 (CHEST-1) was a 16-week multicenter, randomized, double blind, placebo-controlled study that investigated the efficacy and side effect profile of riociguat in patients with CTEPH who were deemed inoperable or who had persistent or recurrent PH after pulmonary endarterectomy.[14] The CTEPH subjects were adjudicated to be technically inoperable by a steering committee that included experienced surgeons from established CTEPH centers. At Week 16, the 6MWD had increased from baseline by a mean of 39 meters in the riociguat group, as compared with a mean decrease of 6 meters in the placebo group (least-squares mean difference, 46 meters; 95% confidence interval [CI], 25 to 67; $P<0.001$). There were also significant improvements in pulmonary hemodynamics, functional class, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, and a quality of life questionnaire. As in PATENT-1, riociguat was well tolerated. The most clinically significant drug-related adverse event in riociguat-treated patients is hypotension, and drug titration with biweekly monitoring of systemic blood pressure is recommended. Based on the 2 pivotal trials (PATENT-1 and CHEST-1), the FDA approved riociguat to treat PAH and inoperable or persistent/recurrent CTEPH.

Balloon pulmonary angioplasty (BPA) has been proposed as an alternative invasive experimental procedure in CTEPH patients not amenable to surgery,[15] based on several case reports suggesting a good efficacy/safety profile. In 20 consecutive patients with inoperable or recurrent CTEPH, BPA

produced significant hemodynamic improvements, including decreased mean pulmonary artery (PA) pressure (45±11 mm Hg vs 33±10 mm Hg; $P<0.001$) and increased cardiac output (4.9±1.6 L/min vs 5.4±1.9 L/min; $P=0.011$), improvements in plasma levels of NT-proBNP and troponin T, functional class (3.0±0.5 vs 2.0±0.5; $P<0.001$), and maximal oxygen uptake with exercise (13.6±5.6 mL/kg/min vs 17.0±6.5 mL/kg/min; $P<0.001$).[15] The most significant complication was reperfusion pulmonary edema. Seventeen patients (85%) were alive after 51±30 months of follow-up. Several studies from Japan reported similar outcomes.[16,17] While BPA is currently performed at only a few specialized centers, it is a potential future option for selected patients with inoperable CTEPH.

Modifications in Treatment Algorithm: Up-Front Combination Therapies

PAH treatment most commonly involves initiation of monotherapy, with subsequent escalation (addition of a second and/or a third) drug when patients are not adequately controlled. However, this sequential approach has had limited success.[18-20] It has been postulated that up-front combination therapy targeting the different pathways involved in the pathogenesis of PAH may be more beneficial to patients with moderate to severe PAH. Sitbon et al[21] reported retrospectively on 19 newly diagnosed PAH patients who presented in functional class III/IV and were initiated on up-front triple combination therapy (IV epoprostenol, bosentan, and sildenafil). Significant improvements in 6MWD and hemodynamics were observed after 4 months of treatment in 18 patients ($P<0.01$); 17 patients had symptomatically improved to functional class I or II. At the final evaluation (mean±SD 32±19 months), all 18 patients had sustained clinical and hemodynamic improvement. Overall survival estimates for the triple combination cohort were 100% at 1, 2, and 3 years. Based on experience with up-front combination therapy in several experienced PH centers, the current recommendations include initiation of up-front combination therapy in severe PAH patients (recommendation IIb, level C).[22] But the question remains whether the up-front combination approach should be applied to less severe PAH patients: for example, whether an up-front dual oral therapy is associated with better outcomes than monotherapy. This question will be answered by the Phase 3 multicenter, event-driven study comparing the effects of ambrisentan and tadalafil vs either monotherapy alone, with the primary outcome of time to clinical failure (AMBITION).[23] Secondary endpoints include change in 6MWD, functional class, and percentage of subjects with unsatisfactory clinical response. The trial has recently concluded and results should be announced shortly.

ADDRESSING NOVEL SIGNALING PATHWAYS

Targeting the 3 main pathways, whether as monotherapy or in combination, has most likely resulted in improved outcome of PAH patients. Nevertheless, overall mortality in PAH is still poor. Estimates of 1-, 3-, 5-, and 7-year survival from diagnosis in the largest US-based registry was 85%, 68%, 57%, and 49%, respectively.[24] Therefore, there is an unmet need to discover and develop therapies that involve novel targets.

Enhancing Abnormal Bone Morphogenetic Protein Receptor 2 Pathway

Germline mutations causing loss of bone morphogenetic protein receptor 2 (BMPR2) function are found in >80% of familial and approximately 20% of sporadic cases of idiopathic PAH (IPAH).[25] In addition, patients with IPAH without a BMPR2 mutation or with PAH associated with other conditions have reduced expression of BMPR2 in pulmonary arteries.[26] Since clinical application of BMPR2 gene therapy poses challenges, investigators applied a high-throughput assay to screen available libraries and identified tacrolimus (FK506), an FDA-approved immunosuppressive drug, to increase signaling through the BMPR2 pathway.[27] In PA endothelial cells from IPAH patients, low-dose FK506 reversed dysfunctional BMPR2 signaling. In mice with conditional BMPR2 deletion in endothelial cells and in 2 experimental models of PH in rats, low-dose FK506 attenuated PH. As a result of in vitro and in vivo studies, a Phase 2 placebo-controlled, single-center study is currently being conducted to assess the safety and efficacy of FK506 in PAH patients.[28]

Modifying Oxidative Stress in PAH

PAH is characterized not only by proliferation and apoptosis resistance, but also by abnormalities in glucose oxidation, suggesting a global metabolic disturbance with enhancement of oxidative stress. Apoptosis-signal regulating kinase 1 (ASK1) is a ubiquitously expressed serine/treonine kinase that mediates oxidative stress-induced injury and mediates inflammation, fibrosis, vascular dysfunction, and cellular proliferation.[29] ASK1 inhibition reduced PA pressure, decreased right ventricular and vascular remodeling, and improved right ventricular function in the rat monocrotaline model of PH.[30] Based on experimental data favoring inhibition of ASK1 in PAH, a Phase 2 clinical trial testing the safety and efficacy of an ASK1 inhibitor is underway.

A Novel Role of Mineralocorticoid Receptor in PAH

Mineralocorticoid receptor (MR), a steroid-hormone-activated transcription factor, plays a substantial role in cardiovascular diseases. MR antagonists have long been appreciated as effective treatments for heart failure and hypertension. However, recent research suggests that PAH patients may also benefit from MR antagomism. In 3 distinct experimental rodent models of PH, MR antagonism attenuated the severity of the PH phenotype.[31,32] MR blockade initiated at the time of the PH stimulus prevents pulmonary vascular hyperplasia and rise in right ventricular systolic pressure. More importantly, initiation of MR antagonism after establishment of experimental PH attenuates the progression of disease, supporting a potential for these drugs to be used therapeutically. Mechanistic studies revealed that MR is functional in distal PA smooth muscle cells and that MR inhi-

bition prevents cell proliferation. Exposure of PA smooth muscle cells to hypoxia or to platelet-derived growth factor promotes translocation of MR to the nucleus, whereas MR antagonism blocks the proliferative effects of these PH activators.[32] In addition, in PA endothelial cells, aldosterone-induced oxidative stress impairs endothelin-B receptor signal transduction, resulting in impaired NO synthesis.[31] Collectively, these recent results support the notion that MR contributes to the development and worsening of pulmonary vascular remodeling and elevation of pulmonary pressure in PAH. Since MR antagonists are available and their safety profile is well characterized—even in patients with advanced heart failure—they may be a novel therapeutic target for PAH. Indeed, 2 Phase 2 trials are underway: one testing the effect of spironolactone therapy on exercise capacity and endothelial dysfunction in PAH,[33] and another testing the effect of spironolactone on collagen metabolism in PAH.[34]

NOT ALL SUCCESS

The development of novel therapies for PAH is intimately linked with understanding the pathogenetic sequelae. Although great progress has been made, more work remains to be able to decipher the molecular pathways that differentially drive the various vascular phenotypes. In addition, our experimental models of PH do not closely resemble human disease. It is, therefore, not surprising that several attempts at drug discovery, although supported by in vitro and in vivo animal data, have not been successful. A few examples include terguride, an oral, potent serotonin ($5\text{-}HT_{2A}$ and $5\text{-}HT_{2B}$) receptor antagonist. Serotonin is a signaling molecule that stimulates proliferation of pulmonary vascular smooth muscle cells and constriction of the vessel wall, which can induce PAH. A double-blind, randomized Phase 2a study showed no significant effect of terguride compared with placebo on hemodynamics or secondary endpoints, and the rate of severe and serious adverse events was higher with terguride.[35] Another example is imatinib, a tyrosine kinase inhibitor used to treat chronic myelogenous leukemia. In humans, several case reports have shown promising results for imatinib as a treatment for PAH.[36,37] A Phase 2 study in patients with PAH failed to achieve the main outcome (6MWD), but a post-hoc analysis demonstrated improvements in 6MWD and hemodynamics in those patients treated with imatinib who had a baseline pulmonary vascular resistance $\geq$1000 dyn·s·cm^{-5}.[38] The Phase 3 placebo-controlled trial demonstrated a significant improvement in 6MWD (main outcome) and hemodynamics with imatinib vs placebo, while time to clinical worsening was more often encountered in the active arm, and discontinuations due to serious adverse events were more frequent with imatinib.[39] Based on the safety profile suggesting an increased risk of intracranial hemorrhage with imatinib in PAH patients, the drug has not been approved to treat PAH at this time. Lastly, aspirin (as an antiplatelet agent) and simvastatin (which positively affects both pulmonary endothelial and smooth muscle cells in experimental models of PH) were hypothesized to be beneficial in PAH. A randomized, double-blind, placebo-controlled clinical trial of aspirin and simvastatin in patients with PAH receiving background therapy showed no significant difference in the 6MWD at 6 months between aspirin or simvastatin and placebo arms.[40] Major bleeding episodes were encountered more often with aspirin than with placebo.

CONCLUSION

This is an exciting time for clinicians and scientists involved in PAH research, as several promising therapeutic options are in development for the treatment of this fatal disease. Major advances have been made, with the introduction of novel compounds such as macitentan, riociguat, and oral treprostinil, which target the 3 key pathways (endothelin, NO, and prostacyclin, respectively) involved in the pathogenesis and progression of PAH. In addition, clinical trial design in PAH has evolved from short-term studies with 6MWD as the sole primary endpoint, and new compounds are being tested in long-term event-driven trials. A number of important clinical trials in PAH are underway, the results of which are eagerly anticipated. Based on the great effort and activity in this field, it is hoped that, in the not too distant future, new treatments and new algorithms will be available that will improve the prognosis for patients with PAH.

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