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New Trial Designs and Potential Therapies for Pulmonary Artery Hypertension

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A greater understanding of the epidemiology, pathogenesis, and pathophysiology of pulmonary artery hypertension (PAH) has led to significant advances, but the disease remains fatal. Treatment options are neither universally available nor always effective, underscoring the need for development of novel therapies and therapeutic strategies. Clinical trials to date have provided evidence of efficacy, but were limited in evaluating the scope and duration of treatment effects. Numerous potential targets in varied stages of drug development exist, in addition to novel uses of familiar therapies. The pursuit of gene and cell-based therapy continues, and device use to help acute deterioration and chronic management is emerging. This rapid surge of drug development has led to multicenter pivotal clinical trials and has resulted in novel ethical and global clinical trial concerns. This paper will provide an overview of the opportunities and challenges that await the development of novel treatments for PAH. (J Am Coll Cardiol 2013;62:D82–91) © 2013 by the American College of Cardiology Foundation

A greater understanding of the epidemiology, pathogenesis, and pathophysiology of pulmonary artery hypertension (PAH) has led to significant advances over the past 2 decades in treatment of this disorder. However, these treatment options are neither universally available nor always effective, underscoring the need for development of novel therapies and therapeutic strategies. Because PAH is considered an orphan disease that is uniformly progressive and fatal, prior clinical trials evaluating novel therapies were relatively short in duration and were comprised of small populations of affected patients. These studies provided evidence of efficacy, but were limited in evaluating the scope and duration of treatment effects. Accordingly, clinical development of novel therapies for PAH in the future will require trials of larger and perhaps more diverse patient cohorts who are studied for longer periods and with more robust and meaningful efficacy endpoints. The challenges posed by these requirements are substantial, and include

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greater global access to patients and experienced investigators, industry partners who are willing and able to invest in drug development for a rare disease, and collaboration with regulators to ensure that the trials can both provide evidence of sufficient safety and efficacy to support regulatory approval while, at the same time, can be realistically carried out in a diverse clinical environment. This paper will provide an overview of the opportunities and challenges that await the development of novel treatments for PAH.

Designs and Endpoints for PAH Trials

Clinical trial designs. The objective of clinical trials is to determine, in a selected population, if a treatment is both safe and effective and whether the findings in the study can be translated to the larger population of affected individuals. The "proof of concept" or phase 2 stage of clinical development can generate critical information regarding dosing and safety and can provide insight into whether a full-scale phase 3 study is likely to be successful (1). Virtually all of the currently approved PAH therapies underwent phase 2 studies prior to phase 3, whereas none of the drugs that have gone straight to pivotal trials has met with regulatory approval.

Nonetheless, the limitations of phase 2 trials include: small sample size, heterogeneity of the study population, selection of an appropriate endpoint, and competition for patients between multiple trials. Some of these issues can be addressed by using enrichment strategies, as recently highlighted in the Food and Drug Administration's strategies for successful drug trials (2). One of the challenges arising from our relative success in developing therapies for PAH is that future therapies can no longer be studied as de novo treatments with placebo-treated comparator groups. One solution to this dilemma is to implement creative adaptive designs. For example, a factorial design allows for testing more than 1 novel element in a single trial (3).

A second creative approach that could be used for PAH therapies, which is known to be effective during the short term but without potential utility over a longer term, is the randomized discontinuation trial. Although PAH clinicians have expressed concern about implementing this approach in a population that is hemodynamically fragile, the standardized use of background therapy should help minimize the risk without compromising the quality of information. This trial design utilizes predictive enrichment techniques by selecting subjects for study who, on the basis of their prior response, have the greatest chance of benefit (4). Of course, concern remains that withdrawal of a treatment could result in acute clinical deterioration (5). Additionally, it is problematic that the population studied in this type of trial design may not be representative of the larger affected population (4).

Noninferiority and crossover designs are difficult to implement in an orphan disease. A noninferiority trial utilizing current endpoints could require large sample sizes (6). Acceptable margins for such studies would be dependent on many factors, including the selected endpoint, the active control regimen, the eligibility criteria, and supportive care regimens, and these may be difficult to justify in settings such as PAH where these factors are rapidly changing (6–8). A crossover design can test for short-term differences in 2 different treatment approaches; however, such designs assume that a short time to wash out the therapeutic is adequate and that there are no "carry-over" treatment effects (3). Crossover trials for PAH are of concern as a washout may cause rebound clinical worsening.

Clinical trial endpoints. CHARACTERISTICS OF APPROPRIATE PRIMARY ENDPOINTS IN REGISTRATION TRIALS. The selection of the primary endpoint for a registration trial is one of the most important steps in study design at any phase of development. There are several characteristics of outcome measures that should be considered when choosing the primary endpoint. This endpoint should be consistently and reliably measureable, because missing data meaningfully impacts the interpretability of results and because ethical issues might arise when outcome assessments are based on invasive procedures that are not routinely conducted as part of clinical practice. These ethical issues are particularly important in pediatric settings. Due to these considerations, endpoints that require right heart catheterizations or histologic measures that require invasive biopsy procedures might be problematic. The outcome measure also should be distinct and reliable, with properly established content validity. Content validity is "the extent to which an instrument measures the important aspects of concepts most significant and relevant to the patient's condition and its treatment" (9,10).

The most important characteristic of the primary outcome measure in a registration trial is that it should be a clinically meaningful endpoint, defined by Temple (11) to be a direct measure of how a patient "feels, functions or survives," where "function" refers to the ability of a patient to carry out normal daily activities. Examples of clinically meaningful endpoints in PAH are death, lung transplantation, initiation of parenteral prostanoid therapy, hospitalization for worsening PAH, or symptoms of PAH such as cough, breathlessness, chest pain, or syncope. PAH symptoms can be utilized as primary endpoints in

Abbreviations and Acronyms

6MWD = 6-min walk distance
ECMO = extracorporeal membrane oxygenation
eNOS = endothelial nitric oxide synthase
EPC = endothelial progenitor cell
FAO = fatty acid oxygenation
LV = left ventricle/ventricular
MSC = mesenchymal stem cell
NO = nitric oxide
PAH = pulmonary arterial hypertension
PDGF = platelet-derived growth factor
PH = pulmonary hypertension
PRO = patient-reported outcome
PVR = pulmonary vascular resistance
RAAS = renin-angiotensin-aldosterone system
RV = right ventricle/ventricular
TTCW = time to clinical worsening
VEGF = vascular endothelial growth factor

Table 1 Future Therapeutics

Pathway/Targets	Therapy
Vasodilation	Nitric oxide, nitrite
Sympathetic nervous system	Selective > nonselective beta-adrenergic blockade
Renin-angiotensin-aldosterone system	Aldosterone antagonist, vasopressin receptor antagonist, catheter-guided ablation
Vascular remodeling—metabolic alterations	Dichloroacetate, ranolazine
Anti-inflammation	Rho-kinase inhibitors, rituximab, vasoactive intestinal peptide
Selective and multikinase inhibition	Tyrosine kinase inhibitors
Stem cells	
Gene therapy	
Cell therapy	Endothelial, mesenchymal, and gene-enhancing cells
Devices	Cardiac resynchronization, extracorporeal life support: venoarterial, venovenous, and pumpless arteriovenous extracorporeal lung assist

registration trials if the effects on these outcomes are assessed using appropriate patient-reported outcome (PRO) measures. The December 2009 Food and Drug Administration's Guidance to Industry for Patient-Reported Outcomes provides valuable insights into the proper development of such measures, including confirmation of reliability, sensitivity, content and construct validity, interpretability, and clinical relevance (12). To ensure integrity of the evaluation of the effect of an intervention on symptoms of PAH, it is important that this be done using randomized blinded clinical trials with efforts to minimize the occurrence of missing data. In pediatric settings, it might be necessary to restrict trials to children ≥7 years of age when conducting a PRO-based assessment of treatment effects on PAH symptoms.

SURROGATE ENDPOINTS: DEFINITION AND VALIDATION. In order to reduce the size and duration of registration clinical trials, there often is interest in using indirect outcome measures, such as biomarkers that are measurements of biological processes, as replacement or "surrogate" endpoints. A surrogate endpoint is an outcome measure "used as a substitute for a clinically meaningful endpoint" (11). It is acceptable to use an indirect outcome measure if it is a properly validated surrogate for a clinically meaningful endpoint. Establishing an indirect measure to be a valid surrogate endpoint "requires providing an evidence based justification, often from randomized controlled clinical trials, that achievement of substantial effects on the surrogate endpoint reliably predicts achievement of clinically important effects on a clinically meaningful endpoint" (13).

Biomarkers that are based on laboratory assessments (such as brain natriuretic peptide or the N-terminal pro-brain natriuretic peptide) or hemodynamic measures (such as pulmonary vascular resistance [PVR], PVR index, mean pulmonary arterial pressure, or cardiac output) are of interest as potential surrogate endpoints because they are thought to be related to disease progression and because they are known to be correlated with clinically meaningful endpoints. As correlates, they can be very useful for diagnosis or assessing prognosis, as endpoints in phase 2 trials, or as parameters that support the meaningfulness of changes in the primary endpoint. In addition, measurement of biomarkers may provide insights into the mechanisms of action of novel treatments.

It is important, however, to distinguish between showing that a biomarker value is strongly correlated with the risk of achieving clinically meaningful endpoints and demonstrating that changes in biomarker values reliably predict comparable directional changes on clinically meaningful outcomes; in other words, a "correlate does not a surrogate make" (14). There are multiple reasons for this apparent paradox (13–15). First, even if a biomarker does not contribute to causation of the disease, it may nevertheless be correlated with a clinically meaningful endpoint if both the endpoint and biomarker are impacted by the disease's true cause. Second, the magnitude of change and duration of effect on the biomarker that translates to clinically meaningful endpoints may be unknown, or there may be other pathways that are not represented by the biomarker. Third, even if the biomarker captures the effects of the intervention on all important causal pathways of the disease process, interventions often have off-target effects that are not captured by the biomarker, yet may have a meaningful impact on the net treatment effect (14). The Institute of Medicine provided a detailed discussion of rigorous steps, entitled "analytical validation," "qualification," and "utilization," that are needed before a biomarker is used as a replacement endpoint in any registration clinical trial (15). Unfortunately, it is very uncommon to have biomarkers that are properly validated surrogate endpoints, and it is apparent that there are currently none in the setting of PAH.

INDIRECT OUTCOME MEASURES. Some indirect measures that are dependent on patient motivation or clinical judgment have been used as primary endpoints in registration trials. These include the 6-min walk distance (6MWD), the 3-min stair climb, and handgrip strength or treadmill testing. These tests are conducted in artificial settings and thus provide only indirect assessments of the effect of the intervention on how a patient feels, functions, or survives (13). What is the minimal clinically meaningful effect of treatment on 6MWD, that is, the treatment-induced change that can be translated to a patient's ability to carry out daily activities that are relevant to him or her? As trials in the future will primarily assess the effects of add-on therapy to background therapies, the magnitude of incremental changes in 6MWD will be narrower than studies in treatment-naïve patients, making interpretation more challenging. In pediatric settings, these indirect measures might also require an age restriction, as younger subjects may not be able to cooperate sufficiently.

THE ROLE AND INTERPRETABILITY OF COMPOSITE ENDPOINTS. Composite endpoints may more comprehensively reflect

clinically meaningful treatment effects. This approach is particularly appealing in rare diseases such as PAH and, in particular, in subsets of rare diseases such as PAH in children. All of the components of a composite endpoint should be of similar clinical relevance, thereby strengthening the meaningfulness of the treatment effect. For example, the major cardiovascular endpoint is a composite endpoint comprised of cardiovascular death, stroke, and myocardial infarction that is used frequently as the primary endpoint in registration trials for the treatment of acute coronary syndrome. The meaningfulness of changes in this composite endpoint is enhanced because each component is an independent measure of irreversible morbidity or mortality.

In PAH, the composite endpoint of time to clinical worsening (TTCW) has been used as a secondary, or reinforcing, endpoint in prior registration trials. As defined at the Fourth World Symposium in PH at Dana Point, California, components of this composite include death, lung transplantation, hospitalization for worsening PAH (including atrial septostomy), initiation of intravenous therapy due to worsening PAH, and worsening of function (i.e., worsening World Health Organization functional class and a decrease in 6MWD). Recently completed trials in PAH suggest that "clinical worsening" may be a more suitable and meaningful primary endpoint than 6MWD, particularly as new trials will be studying patients on background therapies and for longer periods of observation.

ALTERNATIVE ENDPOINTS FOR ADULT AND PEDIATRIC PAH TRIALS. Individual measures that are potential phase 3 trial primary endpoints include:

1. Overall survival (all-cause mortality);
2. Hospitalization for worsening PAH and death caused by PAH;
3. Exercise capacity measures;
4. Functional class; and
5. PROs
   - Level of successful social interactions with peers
   - 36-Item Short Form Health Survey
   - Borg Dyspnea Score
   - Days of work (or "school" in pediatric setting) missed for health-related reasons.

Composite measures are of interest in both adult and pediatric PAH settings. For example, changes in 4 symptom categories comprising the endpoint could be: dyspnea, chest pain, dizziness/syncope, and fatigue/activity level. Properly developed instruments would be needed for the assessment of these symptoms, and the appropriate time post-randomization for endpoint assessment would also need to be defined.

The Dana Point TTCW composite endpoint, which is the time to the first event, could be enhanced to include a component that would be based on these same 4 PAH symptoms cited in the previous text. These symptom variables are especially important as, for PAH, death is rarely the first clinical event. For example, this TTCW composite might be defined as:

1. Death
2. Lung transplantation
3. Hospitalization for worsening PAH (including atrial septostomy)
4. Initiation of intravenous therapy due to worsening PAH
5. Worsening of function (i.e., worsening functional class and exercise capacity)
6. Worsening of PAH symptoms (i.e., worsening of at least 2 of the 4 symptoms: dyspnea, chest pain, dizziness/syncope, fatigue/activity level)

Future Targets for Therapeutics

The future of clinical research in PAH will likely consist of 3 major approaches. First, the identifying and testing of newly identified targets of pathogenesis. Of these, vasoconstriction, inflammation, abnormal growth, and angiogenesis are the most extensively studied at present. Second, optimization of treatment targeting pathways known to be important in PAH, for example, developing more potent, less toxic drugs that target the endothelin, nitric oxide, and prostacyclin pathways, or establishing whether combination therapy is more efficacious than monotherapy and, if so, determining the timing and choice of agents. Third, the development of devices aimed at improving or supporting right ventricular (RV) function. The next section will discuss these in more detail (Table 1).

Vasodilators. NITRIC OXIDE. Nitric oxide (NO) is a potent vasodilator and an inhibitor of platelet activation and vascular smooth muscle proliferation. Intact NO signaling is critical to maintaining the appropriate pulmonary vascular tone both before and after birth (16). There are 3 isoforms of the NO synthase family of enzymes: endothelial nitric oxide synthase (eNOS), inducible NO synthase, and neuronal NO synthase; all are expressed in the lung (17). Both eNOS and inducible NO synthase deficiency are associated with elevated basal pulmonary vascular tone in animal models (18,19).

Inhaled NO is a familiar agent that is an effective pulmonary vasodilator. Inhaled NO works well in the setting of increased pulmonary vascular tone due to pulmonary vasoconstriction and has minimal effects in healthy subjects (20). Inhaled NO is potentially useful for PAH by limiting RV hypertrophy and enhancing downstream signaling targets, such as soluble guanylate cyclase and cyclic guanosine monophosphate, to attenuate pulmonary vascular remodeling (21–23). Nitrite is a physiological signaling molecule with roles in intravascular endocrine NO transport, hypoxic vasodilation, signaling, and cytoprotection after ischemia-reperfusion. Evaluation of inhaled nitrite for PAH is in progress as well (NCT01431313), understanding that rebound after withdrawal of inhaled NO and inhaled nitrite is a concern.

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Beta-blockers. Unlike left-sided heart failure, the effects of beta-blocker therapy on PAH-induced right heart failure have not been thoroughly investigated (24). Concern regarding the use of beta-blockers in PAH is based primarily on their potential to produce negative inotropic effects; additionally, PAH patients are dependent on heart rate to maintain cardiac output, and these agents are likely to affect this compensatory mechanism (25,26). However, many of the original studies used first-generation, nonselective beta-blockers that have more bronchial and myocardial depressive effects than currently available more selective agents (26,27). In support of further study of their use in PAH is the demonstration that chronic adrenergic overdrive, which is present in PAH, can result in myocardial depression and cardiac compromise (28).

In animal models of PH, selective beta-blockers appear to improve RV function and myocardial remodeling (29,30). For example, carvedilol (α1/β1/β2-adrenergic receptor antagonist) improved RV contractility and hemodynamics in the Su-5416 (sugen)/hypoxia derived PAH-rat model (30), and bisoprolol (cardioselective β1-adrenergic receptor antagonist) delayed progression toward right heart failure by preventing RV inflammation and decreased RV fibrosis in the monocrotaline PAH rat model (31). A phase 2 clinical study to investigate the safety and efficacy of bisoprolol in PAH patients (NCT01246037) has been initiated.

Sympathetic nervous system and renin-angiotensin-aldosterone system. The sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) are both activated in PAH patients, but the value of these systems as therapeutic targets is unclear (32,33). Hyponatremia is an indirect marker of RAAS activation and may be a useful surrogate biomarker of disease severity (33). Aldosterone inhibition reduces pulmonary pressure and pulmonary vascular resistance without systemic hypotension in the Su-5416/hypoxia and monocrotaline animal models (34). These studies provide support for the evaluation of aldosterone antagonist therapy in PAH (NCT01712620).

The release of arginine vasopressin is an additional factor contributing the sodium and water retention that is common in PAH. In patients with heart failure, plasma arginine vasopressin levels are elevated out of proportion to serum osmolarity, resulting in water retention and hyponatremia (35,36). Conivaptan, a vasopressin receptor antagonist, improves signs of left heart failure and is being studied in the treatment of PAH-induced right heart failure (NCT00811486).

Catheter-guided ablation to alter the RAAS pathway is also being investigated for PAH. Pulmonary vein ablation has been used to treat resistant atrial fibrillation, and more recently, renal sympathetic nerve ablation has shown promise in the treatment of refractory systemic hypertension (37). A recent pilot study from China demonstrated marked reductions in pulmonary artery pressure and vascular resistance in 13 PAH patients after catheter-based denervation of the pulmonary artery (38), but this has not yet been confirmed by other investigators.

Vascular remodeling. METABOLIC ALTERATIONS: DICHLOROACETATE. The vascular remodeling in PAH is partially characterized by a state of apoptosis resistance. As in cancer, a switch from the antiapoptotic glycolytic metabolism to the pro-apoptotic oxidative phosphorylation metabolism causes regression of vascular remodeling in several PH animal models (39–41). Mitochondrial-metabolic abnormalities have been proposed in PAH, including disruption in pyruvate dehydrogenase kinase-mediated inhibition of pyruvate dehydrogenase, which increases aerobic glycolysis in the lungs and RV (42). By inhibiting mitochondrial pyruvate dehydrogenase kinase and pyruvate dehydrogenase, dichloroacetate increases pyruvate entry into the mitochondria, promotes glucose oxidation over glycolysis (39), and restores Kv channel function and expression in pulmonary artery smooth muscle cells, leading to the inhibition of voltage-gated calcium channels, a decrease in intracellular calcium, an inhibition of vasoconstriction, and a reduction in pulmonary artery smooth muscle cell proliferation (43–45). Based on PH regression in animal models (43,44), a phase 1, safety and tolerability, 2-center study of dichloroacetate in functional class III to IV PAH patients on background therapy is ongoing in Canada and in England (NCT01083524).

METABOLIC ALTERATIONS: RANOLAZINE. Reactivation of pyruvate dehydrogenase kinase to promote glucose oxidation can be achieved by activating the Randle cycle, using inhibitors of fatty acid oxidation (FAO) (42). FAO is increased in RV hypertrophy produced by pulmonary arterial banding in animals (46). Accordingly, it has been proposed that agents that inhibit FAO could improve RV hemodynamics in PAH. Ranolazine, an FAO inhibitor approved to treat refractory angina, improves cardiac work by inhibiting FAO through activation of pyruvate dehydrogenase and stimulating glucose oxidation (47,48). An acute, randomized, placebo-controlled, single-center safety and efficacy study with ranolazine for PAH is currently enrolling in the United States (NCT01757808).

Anti-inflammatory agents. Inflammation occurs in PAH with different levels of severity dependent on the subtype. Mononuclear cells, including T cells, B cells, and macrophages, surround plexiform lesions in pathologic specimens. Clinically, PAH patients have elevated cytokine levels of interleukin-1B, -6, and -8 and chemokines CCL2/MCP-1, CCL5/RANTES CX3CCL-1, and CXC3CL1/fractalline (49–54).

RHO-KINASE INHIBITORS. A wide variety of cellular actions, including proliferation, apoptosis, motility, migration, inflammation, and vasoconstriction, are influenced and regulated by the Rho/Rho-kinase signaling pathway (55,56), a pathway that appears to play an important pathogenetic role in PH (57). Rho/Rho-kinase inhibitors, such as fasudil and Y-27632, effectively inhibit the development of PH when administered to animals prior to the induction of PH; when given to animals with established PH, these agents improve endothelial cell function, decrease arterial

neomuscularization, and improve RV function (58–60). Small studies evaluating fasudil in PAH thus far have demonstrated a nonselective reduction in both pulmonary and systemic vascular resistances (58,61,62). This potential decrease in systemic blood pressure is of concern and requires careful consideration during its drug development.

RITUXIMAB. Rituximab is a chimeric monoclonal antibody that binds the B-cell surface protein CD20. It has proven efficacy in a number of diseases characterized by increased B-cell numbers or aberrant function, including lymphomas, leukemias, and autoimmune disorders (63,64). The potential role of autoimmune and inflammatory mechanisms in PAH has raised interest in the use of rituximab in PAH, and specifically in the treatment of sclerodema-associated PAH. Since infusion of rituximab can result in hypotension, this will be a closely watched potential adverse event in a trial currently in progress (NCT01086540).

VASOACTIVE INTESTINAL PEPTIDE. Vasoactive intestinal peptide (VIP) is a neuropeptide in the glucagon growth hormone-releasing factor secretion superfamily with a wide range of effects, including anti-inflammatory and immune-modulatory roles as well as vasodilation of the pulmonary vasculature and inhibition of pulmonary artery smooth muscle cell proliferation (65–67). Administration of VIP to patients with PAH by inhalation improved hemodynamics and exercise tolerance in a small, uncontrolled 3-month study (68). However, a randomized, placebo-controlled, double-blinded phase 2 trial showed no effects of inhaled VIP in the doses studied (69,70).

Tyrosine kinase inhibitors. Tyrosine kinase inhibitors (TKIs) are pharmaceutical agents derived to inhibit tyrosine kinases, and a number of these agents have proven to be markedly effective antitumor and antileukemic treatments (71). PAH and cancer share elements of pathophysiology. As part of the pulmonary vascular remodeling, endothelial cells in a monoclonal expansion form plexiform lesions that express angiogenic vascular endothelial growth factor (VEGF) and VEGF receptors. The cells become resistant to apoptosis and contribute to the microvascular obstruction. Thus, cross-purposing anticancer therapies for PAH is an opportunity for novel therapeutics.

Imatinib is an example of such an agent that has completed phase 3 development for advanced PAH. It is a well-established inhibitor of the kinase BCR-ABL, the receptor for the stem cell factor c-KIT and the platelet derived growth factor (PDGF) receptor (72), and it is approved for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors (73,74). Because of the putative role of PDGF in the development of PAH, this agent has been investigated as a possible therapeutic agent for PH (75,76).

In the IMPRES (Imatinib in Pulmonary Arterial Hypertension, a Randomized Efficacy Study) (77), a multicenter, randomized, placebo-controlled trial of imatinib for the treatment of PAH, patients had modest improvements in 6MWD and reductions in PVR with no differences in TTCW or survival between groups; but, of particular concern, subdural hematomas occurred in 8 patients in the treatment arm (2 in the core study and 6 in the extension study). As a result, development of imatinib for PAH has been discontinued.

The multikinase inhibition, by definition, can add to the off-target effects of these drugs, which may be unpredictable and devastating (78). Sorafenib, a Raf-1, VEGF-R2, and PDGF receptor-b inhibitor evaluated in a phase 1 dosing safety study, demonstrated some improvement in exercise capacity but no improvement in cardiac output (79), and development of sunitinib for PAH was halted after drug-induced cardiotoxicity was observed in oncology trials.

Cardiotoxicity with TKIs is a serious concern, with reports of cardiac ischemia, left ventricular (LV) dysfunction, and hypertension occurring with VEGF inhibition and as an off-target consequence (80–87). LV dysfunction is potentially fatal in a PAH patient, and is difficult to diagnose prior to symptoms. Research of the oncology data demonstrates often idiosyncratic, nondose-dependent decreases in cardiac function with sunitinib, sorafenib, and imatinib (81,83–87). Adding to this concern are case reports implicating the multi-TKI dasatinib as a potential inducer of PAH (88).

Stem cells. Regeneration of lung microvasculature is a novel therapeutic strategy for restoring pulmonary hemodynamics in patients with advanced PAH. Evidence in experimental models of lung vascular disease has suggested that, as in systemic arterial beds, stem cells may also induce the regeneration of pulmonary microvessels. The administration of mesenchymal stem cells (MSCs) may be a therapeutic option for PAH. Despite the progress in stem cell biology, a number of hurdles still need to be overcome, including the difficulty of ex vivo expansion, the poor delivery efficiency (<5% of transplanted cells are retained after transplantation), and their uncertain fate in vivo.

Gene therapy. The pulmonary endothelium is accessible through the pulmonary and bronchial circulations, whereas the epithelial linings of alveoli can be accessed through the airways. The pathology of PH suggests several distinct genetic targets; gene therapy delivered through either the airway or vasculature may be feasible.

Cell therapy. Both endothelial progenitor cells (EPCs) and MSCs have been evaluated in pre-clinical studies as therapy for PAH on the basis of their abilities to repair and regenerate damaged pulmonary vasculature. A small clinical trial using autologous EPCs showed improvements of both pulmonary hemodynamics and clinical performance (6MWD) (89). MSCs allow for allogeneic cell therapy because they are considered immune privileged. However, in contrast to EPCs, there have been no human studies evaluating MSC transplantation in established PAH.

GENE-ENHANCED CELL THERAPY. MSCs may represent a more convenient platform for cell-based gene therapy as a result of their potential for allogeneic transplantation as well as their ability to expand in culture.

The use of syngeneic bone marrow–derived early-outgrowth EPCs engineered to overexpress eNOS may represent an innovative approach to improving the function of pulmonary endothelium. Early outgrowth EPCs overexpressing eNOS not only prevented the progression of PAH, but also reversed established disease in the MCT rat model, even when delivered 3 weeks after MCT injury (90). These studies provided evidence to support a phase 1 clinical trial using autologous EPC-based eNOS gene therapy, PHACeT (Pulmonary Hypertension and eNOS Cell Therapy Trial; NCT00469027).

Devices. CARDIAC RESYNCHRONIZATION THERAPY. Ventricular dyssynchrony is seen in progressive stages of PAH-induced right heart failure. PAH patients with severe disease have interventricular mechanical asynchrony, evidenced by delayed peak shortening and prolonged duration of shortening of the RV free wall compared with LV free wall (91). This pattern of interventricular dyssynchrony in PAH is associated with impaired RV systolic function (RV overload) and LV underfilling. Recent work performed in experimental models of PAH suggest that RV free wall pacing improves right heart function (increased maximal rate of rise of RV pressure) and diminishes adverse interventricular diastolic interaction (without detrimental effects on LV or coronary perfusion), thereby potentially delaying development of RV failure (92). These acute changes have recently been confirmed in a pilot study of patients with right heart failure and ventricular asynchrony due to chronic thromboembolic PH (93).

EXTRACORPOREAL LIFE SUPPORT. Cardiogenic shock in PAH patients is an acute decompensation of their underlying chronic RV failure. The use of extracorporeal life support as a bridge to recovery and/or as a bridge to lung transplantation is now clinically utilized (94). The 3 most common extracorporeal life support approaches include: 1) venoarterial extracorporeal membrane oxygenation (ECMO) for hypoxia or hemodynamic failure; 2) venovenous ECMO for hypercapnia or hypoxemia; and 3) pumpless arteriovenous extracorporeal lung assist (Novalung, Hechingen, Germany). ECMO is predominantly used for intubated patients, but it can be used in awake, non-intubated patients as a bridge to transplantation (95–97). A venovenous ECMO experience early in acute RV failure may prove beneficial and, with the Avalon Elite Bicaval Dual Lumen catheter (Avalon Laboratories, Los Angeles, California) allowing a single cannulation site, can avoid multiple access sites and the need for ECMO (98,99). The Novalung assist device is a pumpless, low resistance oxygenator designed for pulsatile blood flow drive by the patient's cardiac output (100). The Novalung device is connected between the pulmonary artery and the left atrium, producing an oxygenated right-to-left shunt, reducing RV afterload (94,95). After the procedure, patients can be ambulatory while awaiting lung transplantation. The main disadvantages are a sternotomy for central cannulation, often with the need for bypass stabilization, and the risk of bleeding, thromboembolism, and infection (94,95).

Ethical/Global Issues in Drug Development for an Orphan Disease

Multicenter pivotal clinical trials in PAH are now being conducted worldwide. Training of centers in less-developed nations on the standards of clinical practice is challenging, not only because of language barriers, but also due to differences in political climates and regulatory practices. In addition, standard of care, facilities, and quality of care is quite diverse. Clinical trial sites must have sufficient manpower and training to ensure that patients' rights and safety are not compromised by trial enrollment (101,102). Many countries have limited funds for treating patients with orphan diseases and, thus, cannot approve all therapeutics.

Summary

There is an ongoing need to develop new treatment strategies for PAH. Advancements in molecular biology and therapeutics have identified novel targets, but not all of these can realistically be studied, given the small number of PAH patients worldwide. New trial designs may enhance the development of new therapies without compromising the adequate assessments of both safety and efficacy. Many of the potential new targets have been identified using animal models of PAH, but these models have thus far not proven to be reliable models of human disease. Other study approaches, such as ex vivo studies of cellular and molecular events from tissue obtained from affected patients, may be more productive in generating new disease pathways to target with new drugs.

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