Building the Case for Novel Clinical Trials in Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance caused by remodeling of distal pulmonary arterioles that occurs as a consequence of a complex interplay between molecular and genetic factors. The incidence of PAH is estimated at 7 to 10 individuals per million people, with a prevalence of ≤50 cases per million. The most recent World Health Organization clinical classification of pulmonary hypertension distinguishes group 1 pulmonary hypertension from pulmonary vascular disease related to lung disease, left atrial hypertension or venothromboembolism by including PAH in association with anorexigen exposure, connective tissue disease, HIV, or portal hypertension, among other specific comorbidities. In turn, idiopathic PAH is diagnosed in patients without a hereditary or other identifiable cause of PAH. Because of the diversity of diseases implicated in the pathogenesis of PAH, an evolving classification among pulmonary hypertension care centers is pathophenotyping patients with pulmonary vascular disease to calibrate suitable therapy.

Before PAH-specific drug treatment availability, diagnosing PAH functioned principally to inform (a dismal) patient prognosis as treatment was relegated primarily to the careful use of warfarin, digoxin, diuretics, and oxygen. The discovery of calcium channel blocker efficacy in this disease was a breakthrough, but this therapy was considered to be appropriate for only a minority of patients, which remains true today. However, subsequent seminal discoveries of key signaling pathways implicated in the pathogenesis of PAH in some patients exposed for the first time disease-specific treatment targets are pathophenotyping patients with pulmonary vascular disease to calibrate suitable therapy.

With the maturation and enhanced availability of applied clinical genomic- and proteomics-based research, the defining features of PAH biology are in continual flux. During the previous few years, numerous molecules that contribute to PAH pathophysiology have been identified in ≥2 experimental animal models of PAH in vivo or in affected patients. Moreover, the pool of potential monogenetic forms of PAH has expanded through the recent identification of novel gene mutations in PAH family clusters. The ramifications of these advances are not inconsequential: the current methods for clinical diagnosis of PAH, which hinge primarily on achieving hemodynamic metrics without regard to other clinical variables, such as right ventricular function or patients’ molecular pathophenotype, are increasingly recognized as antiquated and insufficient.

The National Institutes of Health announced recently a major funding initiative to stimulate investigations that leverage proteomics and genomics for the characterization of pulmonary vascular disease phenotype. Collectively, momentum is shifting in the PAH field toward a personalized medicine approach to disease categorization, diagnosis, and, ultimately, treatment implementation. The barriers to achieving truly individualized care are extensive, complex, and may not be surmountable. Nevertheless, in the spirit of this aim, we believe that PAH is a disease model well suited for smaller trial designs that selectively target patients based on pathobiology (rather than general hemodynamic data alone) and maintain adequate statistical fidelity. Additional potential virtues of these alternative clinical research approaches in PAH include maneuverability between therapies to improve the identification of effective drugs or drug combinations.

The RCT is the principle clinical research method to assess efficacy of novel treatment in PAH and has been instrumental for identifying the vast majority of Food and Drug Administration–approved therapies for this disease. By recruiting clinical resources from PAH centers of excellence worldwide, RCTs have been successful at providing outcome data relevant to this patient population, despite the (relatively) low prevalence of PAH. However, RCTs in PAH trials generally do not incorporate the totality of clinical, genetic, and molecular data when designating inclusion/exclusion criteria...
for enrollment. This, in turn, increases the probability that a study cohort includes a heterogeneous range of PAH substrates, which we believe accounts for inconsistent rates of clinical benefit reported within RCTs as well as across similarly designed RCTs, and, ultimately, limits the translation of clinical trial observations to real-world practice. One often cited justification for the use of conventional RCT design includes unavailability of suitable alternative study designs. Here, we discuss clinical trial designs for the forthcoming era of advanced molecular and genomic PAH diagnosis that maintain rigorous analysis of outcome despite lower patient volume, which are necessary elements of contemporary clinical research studying this heterogeneous and uncommon disease. Although RCTs will continue to play a vital role in PAH research, we believe that we must pivot and start incorporating other designs that will better answer certain questions when a conventional RCT is unlikely to do so.

PAH and Randomized Controlled Trials: An Imperfect Strategy to Study a Complex Disease

Applying RCT Data to Patient Care in PAH

The traditional RCT design hinges on a reductionist approach to establishing patient appropriateness for study consideration, which often involves ≥20 patient inclusion/exclusion criteria for study enrollment. Still, this approach does not seem to offset the heterogeneity of PAH because poor generalizability of findings from RCT to clinical practice are reported. Additional factors specific to traditional study design that are likely to contribute to this dilemma include trial duration variability and flawed study end points.

Optimal Therapy Duration and Ethical Consideration of Placebo Use in PAH Trials

The optimal duration of therapy in PAH clinical trials is unresolved. Although RCTs completed during the past 2 decades have demonstrated that a 12-week end point correlates positively with outcomes assessed in longer extension studies, several PAH studies have included time points ranging from 8 to 26 weeks. Moreover, other trials have demonstrated a benefit at 12 weeks only to observe diminished benefit at 9 months. Data to characterize PAH-specific treatment efficacy as a function of time systemically are unavailable; however, the rapid trajectory of clinical decline in many patients is an important consideration to trial design, especially in the setting of delayed clinical presentation and diagnosis that often characterizes PAH in clinical practice. Recent estimates indicate that despite the availability of PAH-specific therapy, 1-year mortality rates in untreated PAH rival patients with moderate or severe congestive heart failure caused by advanced left-sided heart disease (New York Heart Functional class III/IV; Figure 1). However, clinical trials in systolic heart failure use follow-up periods on a scale of years compared with the much shorter durations commonly used in PAH trials.

Figure 1. Mortality rates in patients with pulmonary arterial hypertension (PAH), left-sided heart failure with reduced ejection fraction (HFrEF), and left-sided heart failure with preserved ejection fraction (HfP EF). A, Kaplan–Meier survival analyses of 6076 patients hospitalized with left-sided heart failure hospitalized during a 15-year period (1987–2001) at Mayo Clinic Hospital (Olmed County, MN). Compared with patients with HfPEF (red line), decreased survival was observed in patients with HFrEF (black line) at 5 years (adjusted hazard ratio for death, 0.96; \( P=0.03 \)). Adapted with permission from Owan et al. Copyright ©2006, the Massachusetts Medical Society. B, Kaplan–Meier analyses compares survival in the contemporary era (2002–2005) for patients with idiopathic, familial, or anorexigen-associated PAH (56 incident and 298 prevalent cases; solid line) with predicted survival data derived from the original National Institutes of Health (NIH) PAH registry. The original NIH PAH registry included 194 patients diagnosed between July 1981 and December 1985 and followed up through August 1988. Adapted with permission from Humbert et al. Copyright ©2010, Wolters Kluver Health. C, Kaplan–Meier analyses from A and B were merged using Adobe Illustrator CS5 on Win7 OS to compare mortality rates from HfPEF (purple dotted line), HFrEF (green solid line), and PAH (observed, blue dotted line; predicted, red line). Graph derived from Humbert et al., D’Alonzo et al., and Owan et al.
In light of the progressive (and generally poor) natural history of untreated PAH, concern has been raised about the ethical implications of placebo use in RCTs, which adds to the complexity of performing controlled clinical studies in this disease. Although the association between placebo use and unanticipated mortality during RCTs in PAH is unresolved, withholding active treatment for the duration of RCTs (12–18 weeks) is associated with a significantly increased short-term risk of morbidity, including clinical worsening. It is notable, however, that, despite these data, up to 50% of patients randomized to placebo in the most recent PAH RCTs were not on background pulmonary vasodilator therapy at all.

End Point Dilemma in PAH Clinical Research
The cornerstone outcome measure to assess intervention efficacy in PAH RCTs has been historically the 6-minute walk test distance. Completion of a RCT powered sufficiently to measure drug effect on other primary end points, such as survival, is uncommon because of the low prevalence of this disease and high costs associated with extended length studies to achieve sufficient statistical power. Although 6-minute walk distance (6-MWD) is proposed as a marker of global health and baseline 6-MWD is an established predictor of survival in PAH, a consistent relationship has never been observed between change from baseline in 6-MWD and survival, PAH-associated hospitalization, or PAH therapy escalation. In addition, although most

Figure 2. Factorial study design used in the aspirin (ASA)-statin (STAT) trial involving patients with pulmonary arterial hypertension (PAH). Patients were randomly assigned in a 1:1:1:1 ratio by a Web-based computerized system to (1) aspirin 81 mg once daily plus simvastatin 40 mg once daily, (2) aspirin 81 mg once daily plus placebo simvastatin once daily, (3) placebo aspirin placebo once daily plus simvastatin 40 mg once daily, or (4) placebo aspirin once daily plus placebo simvastatin once daily. NSAID indicates nonsteroidal anti-inflammatory drug; and PFT, pulmonary function test. Reprinted with permission from Kawut et al. Copyright ©2011, Wolters Kluwer Health.
therapies affect mean 6-MWD to a similar, albeit modest magnitude (≈20–50 m), studies evaluating the effect of prescribed exercise on 6-MWD in PAH demonstrate superior improvements in 6-MWD when compared to PAH pharmacotherapy. These findings underscore the potential bias of the training effect on assessing functional capacity as an outcome measure in this (and other) cardiopulmonary diseases and raises doubt as to the true clinical effect that a small improvement in 6-MWD actually has on PAH outcomes.44 For these reasons, many contemporary study designs in PAH have transitioned away from using 6-MWD as the sole primary end point.15,45 Instead, other clinical end points have been introduced in recently published trials, such as time to the first clinical event related to PAH and time to general clinical worsening.15

Time to clinical worsening, however, may conflict with patients’ clinical care goals by illuminating treatment failure as inevitable. In fact, many professional societies advocate the importance of integrating patient-reported outcomes in clinical research.46 With this in mind, many PAH trials now emphasize patient-reported outcome measurements, such as dyspnea or quality of life. Recently, the Cambridge Pulmonary Hypertension Outcome Review questionnaire was demonstrated to predict clinical deterioration, even after adjusting for functional class and 6-MWD.47 If validated in subsequent studies, the integration of Cambridge Pulmonary Hypertension Outcome Review or similar tools into future trials should be considered.

Investigational end points can inform the pathophysiologic basis for the treatment success or failure. Often, the unavailability of technology and costs limits the widespread use of these end points within RCTs when studied across large populations and different centers. Although such end points are unlikely to serve as the basis for drug approval, the use of investigational end points in future trial designs can help clarify the relevance of basic science or preclinical observations to patients with idiopathic PAH. Examples of this might include changes in pulmonary vascular metabolic status using fluorodeoxyglucose uptake48 or distinguishing adaptive from maladaptive RV structural changes using cardiac MRI. Such an approach to including investigational secondary end points is not without precedent; for example, many historic trials in myocardial infarction and heart failure were designed to achieve the primary clinical end point, while also providing information on disease epidemiology through surrogate end points.49

Clinical Research Designs for PAH: Alternatives to the RCT

Factorial Design

Factorial studies allow investigators to test multiple hypotheses at once. The simplest example is a 2×2 design, where 2 treatments are studied. For example, if studying drug A and drug B, a factorial design would comprise 4 groups: (1) active drug A plus placebo drug B, (2) placebo drug A plus active drug B, (3) placebo drug A plus placebo drug B, and (4) active drug A plus active drug B.

Recommended Transition Period Dose Changes

<table>
<thead>
<tr>
<th>Dose Transition Day</th>
<th>Epoprostenol Dose</th>
<th>Study Drug Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unchanged</td>
<td>10% starting epoprostenol dose</td>
</tr>
<tr>
<td>2</td>
<td>80% starting epoprostenol dose</td>
<td>30% starting epoprostenol dose</td>
</tr>
<tr>
<td>3</td>
<td>60% starting epoprostenol dose</td>
<td>50% starting epoprostenol dose</td>
</tr>
<tr>
<td>4</td>
<td>40% starting epoprostenol dose</td>
<td>70% starting epoprostenol dose</td>
</tr>
<tr>
<td>5</td>
<td>20% starting epoprostenol dose</td>
<td>90% starting epoprostenol dose</td>
</tr>
<tr>
<td>6</td>
<td>5% starting epoprostenol dose</td>
<td>110% starting epoprostenol dose</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>110% starting epoprostenol dose plus additional 5 to 10% as needed</td>
</tr>
<tr>
<td>0*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>0*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>10*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>11*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>12*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>13*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>14*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
</tbody>
</table>

*As needed. Patients must remain hospitalized at least 24 h after epoprostenol dose has been discontinued.

Figure 4. Discontinuation and transition study design in pulmonary arterial hypertension (PAH). In this study, patients with PAH stable on intravenous epoprostenol therapy were transitioned to study drug (subcutaneous treprostinil or placebo, 2:1) during a period of ≤14 days. Patients were hospitalized during the transition period and for ≥24 hours after the epoprostenol infusions were stopped. Patients who did not complete the transition to study drug or who had clinical deterioration were returned to continuous intravenous epoprostenol. Assessments were conducted at baseline, before discharge after the transition period, and at weeks 4 and 8. Reprinted with permission from Rubenfire et al.53 Copyright ©2007, American College of Chest Physicians.
Figure 5. Study design of an 8-week, multicenter, randomized, placebo-controlled withdrawal trial in pulmonary arterial hypertension (PAH). In this randomized discontinuation trial, patients were transitioned from parenteral to inhaled iloprost and the effects of this on safety and outcome were assessed. During time period (a), parenteral prostacyclins are administered comprising intravenous epoprostenol and intravenous/subcutaneous treprostinil. At time point (b), transition day 1 is defined as the start day of inhaled iloprost with intent of discontinuing parenteral prostacyclin therapy. At time point (c), post-transition day 1 is defined as the first day on inhaled iloprost free of parenteral prostacyclin therapy. Depending on the clinical site or patient, there may be no period of concurrent (overlapping) administration of inhaled iloprost and parenteral prostacyclin therapy and, therefore, no transition period. In such cases, transition day 1 is synonymous as post-transition day 1. Po-T, post-transition; and PP, parenteral prostacyclin. Reprinted with permission from Channick et al.54 Copyright @2013, The University of Chicago Press.

drug A plus placebo drug B, (3) placebo drug A plus active drug B, (4) active drug A plus active drug B (Table 111–17,50–53). When deciding on the various therapies to be tested using a factorial design, it is important to consider the potential for drug–drug interaction(s) between each therapy as a confounder.

Using this design, Kawut et al50 conducted a randomized, double-blind, placebo-controlled 2×2 factorial clinical trial of simvastatin and aspirin in patients with PAH receiving background PAH therapy (Figure 2). Subjects were randomly assigned to aspirin 81 mg once daily/simvastatin 40 mg once daily, aspirin 81 mg once daily/simvastatin placebo once daily, aspirin placebo once daily/simvastatin 40 mg once daily, or aspirin placebo once daily/simvastatin placebo once daily in a 1:1:1:1 ratio. Subjects were then evaluated at baseline, week 6, month 3, and month 6. The study was both informative and instructive. Despite demonstrating no significant benefit from either aspirin or statin therapy on 6-MWD at 6 months, findings highlighted the feasibility and role of performing a factorial study in PAH, particularly when different mechanistic pathways are under investigation.

Crossover Study

The crossover study design is divided into specific phases. In phase I, the dependent variable (ie, end point) is assessed at baseline and after randomization to treatment with study drug or placebo for a predetermined duration of time. In phase II, patients are administered therapy opposite to phase I and the end point is reassessed at the completion of the study (Figure 3). Within-subject analyses are performed to compare differences in outcome between the study drug and placebo. Advantages of this trial design include blinding and use of a smaller sample size compared with parallel trial design.20

As discussed previously, PAH is often characterized by rapid clinical deterioration and symptom transition across various stages of disease natural history (ie, exertional intolerance at early stages versus syncope and progressive right heart failure at advanced stages). Thus, crossover studies, in which a proportion of patients are randomized to upfront placebo generally involve patients with moderate symptom burden and do not control for timing of drug initiation. In addition, because of the observation that PAH-specific therapies seem more efficacious in patients with more severe disease, delayed drug therapy may be a confounding factor in the interpretation of crossover study design results in demonstrating drug efficacy in PAH.

Singh et al51 randomized patients with PAH (n=10) and Eisenmenger syndrome (n=10) to receive sildenafil or placebo for 6 weeks and then crossed over to opposite therapy after a washout period of 2 weeks. Sample size calculation was based on a predetermined definition of improvement in 6-MWD by 50 m as clinically relevant, and the primary outcome was compared using repeated-measures ANOVA. The authors also recorded and compared cardiopulmonary hemodynamic changes with Friedman tests. Individual changes in mean pulmonary artery pressure, New York Heart Association functional status, and metabolic equivalents achieved during exercise were analyzed using the Wilcoxon signed-rank test. A benefit for sildenafil use was observed in the studied patient populations, which was later confirmed in larger RCTs.12

Randomized Discontinuation Trial and Withdrawal Studies

A randomized discontinuation trial (RDT) is optimal for studying long-term, noncurative therapies, especially when the use of placebo is considered unethical.52 The RDT consists of 2 phases. In the first phase, all patients are treated with the study drug; in the second phase, drug therapy responders are randomly assigned to switch to placebo or continue the same treatment.52 Predictive enrichment techniques are used to select subjects for study who have the greatest chance
formed by Rubenfire et al., in which clinically stable patients are transitioned safely to an alternative form of therapy. Such RDTs in principle, aim to determine whether patients may benefit because medication nonadherent patients or those reporting adverse events are generally not considered for study enrollment. Withdrawal studies, which are similar to RDTs in principle, aim to determine whether patients may be transitioned safely to an alternative form of therapy. Such a randomized, placebo-controlled withdrawal trial was performed by Rubenfire et al., in which clinically stable patients with PAH on epoprostenol therapy were randomized to transition to subcutaneous treprostinil or placebo in a 2:1 manner during a period of ≤14 days (Figure 4). In this study, of the 8 patients withdrawn to placebo, 7 (88%) had clinical deterioration, whereas only 1 of 14 patients (7%) withdrawn to treprostinil deteriorated (P<0.001).

More recently, Channick et al. used a RDT to assess outcomes after transition from parenteral prostacyclin to inhaled iloprost (Figure 5). In this study of 37 consecutive patients, the transition period began on the first day of inhaled iloprost with intent of discontinuing parenteral prostacyclin and completed on the first day of treatment with inhaled iloprost free of parenteral prostacyclin. Approximately 92% of patients had an overlapping transition with a mean transition period of 10.5±13.9 days. At 1-year follow-up, 78% of the patients remained on inhaled iloprost alone, and 81% were free of clinical worsening. It should be noted, however, that successful transition in this study seemed related to concomitant oral medication use, which must be considered during RDT planning.

An important consideration of this study design in PAH is the possibility for adverse events to occur on therapy withdrawal. Therefore, the RDT planning phase requires particular consideration to the individual patient’s clinical profile, particularly disease severity, when determining appropriateness for RDT trial enrollment.

N-of-1 Clinical Trial

A common N-of-1 trial design involves multiple crossover experiments performed over predefined time periods to compare the effects of different treatments on outcome measure(s) within an individual patient (Figure 6). Although under-represented in the cardiovascular disease literature, Gabler et al. identified 108 N-of-1 trials involving 2154 patients published between 1985 and 2010, which include chronic diseases, such as insomnia, attention deficit hyperactivity disorder, chronic obstructive pulmonary disease, and sleep disordered breathing. In general, after informed consent, a patient enrolled in an N-of-1 trial undergoes baseline measurement of a specific outcome measure. The patient is randomized to receive placebo or a therapeutic agent or placebo and outcomes are assessed at follow-up. Placebo control demonstrates efficacy. Powered adequately to determine effect. Expense. Ethics of placebo use. Subpopulations not well studied.

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Design</th>
<th>Advantage</th>
<th>Limitation</th>
<th>Example in PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial</td>
<td>Patients randomized to study agent or placebo and outcomes assessed at follow-up</td>
<td>Placebo control demonstrates efficacy. Powered adequately to determine effect.</td>
<td>Expense. Ethics of placebo use. Subpopulations not well studied.</td>
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<tr>
<td>Factorial design</td>
<td>≥2 factors, each with ≥2 levels: 2×2 factorial design; drug A+placebo B; placebo A+placebo B; placebo A+active B; active A+active B</td>
<td>Test multiple hypotheses at once. Test combination of agents. Potential interaction between agents.</td>
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<td>Crossover study</td>
<td>Each subject is administered a particular therapy at different time points</td>
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<td>51</td>
<td></td>
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<tr>
<td>Randomized discontinuation trial</td>
<td>Responders to drug therapy are randomly assigned to placebo or continued treatment</td>
<td>Removal of patients who are therapy nonresponders is an element of study design. Adverse events may occur on withdrawal of drug.</td>
<td>53</td>
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<tr>
<td>N-of-1 clinical trial</td>
<td>Multiple crossover experiments over a predefined time period</td>
<td>Individualized therapeutic response identified. Limited statistical power, generalizability of findings to other patients unknown.</td>
<td>None reported.</td>
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PAH indicates pulmonary arterial hypertension.
intervention for a prespecified time period, after which performance on the outcome measure(s) is reassessed. After a drug washout period, the same experimental design is repeated to measure the effect of a second therapy on the same outcome measure(s). Ultimately, a comparison of the effect of each treatment on outcome is performed to characterize drug efficacy. Similar to RCTs, clinicians and patients are generally blinded to the therapeutic agent (or placebo) during the study to avoid the introduction of bias on outcomes. Various permutations in study design involving the number of therapy cycles, duration of therapy, role of blinding, sequence of randomization, and potential for cotherapy are considered according to the disease process and pharmacokinetics of the drug(s) under investigation. Overall, a favorable cost value of an N-of-1 trial compared with RCT is likely, but hinges on the complexity of the selected end points and scale of the comparator RCT (Table 2).

<table>
<thead>
<tr>
<th>Study Element</th>
<th>Randomized Clinical Trial</th>
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<td></td>
<td>Baseline Cost (USD)</td>
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<tr>
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<tr>
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<tr>
<td>Study drug*</td>
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</tr>
<tr>
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</tr>
<tr>
<td>PDE-V (6 wk)</td>
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</tr>
<tr>
<td>ERA+PDE-V (6 wk)</td>
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</tr>
<tr>
<td>Subtotal costs</td>
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</tr>
<tr>
<td>Total costs for trial</td>
<td>2052000.00</td>
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</table>

Published cost estimates for a typical randomized clinical trial (RCT) in idiopathic pulmonary arterial hypertension vary substantially based on several key factors, including study duration, complexity of selected end points, enrollment, and study drug price. Differences in IRB and study drug fees for an N-of-1 trial compared with a RCT reflect the single-center nature of the design and differences in drug treatment duration. 6-MWT indicates 6-minute walk test; ERA, endothelin receptor antagonist; IRB, institutional review board; PDE-V, phosphodiesterase type V; PE, physical examination; and USD, United States Dollars ($).

*Value for study drug costs reflects mean costs for daily study drug use and placebo, based on published costs associated with PDE-V inhibitor class medication.9

intervention for a prespecified time period, after which performance on the outcome measure(s) is reassessed. After a drug washout period, the same experimental design is repeated to measure the effect of a second therapy on the same outcome measure(s). Ultimately, a comparison of the effect of each treatment on outcome is performed to characterize drug efficacy. Similar to RCTs, clinicians and patients are generally blinded to the therapeutic agent (or placebo) during the study to avoid the introduction of bias on outcomes. Various permutations in study design involving the number of therapy cycles, duration of therapy, role of blinding, sequence of randomization, and potential for cotherapy are considered according to the disease process and pharmacokinetics of the drug(s) under investigation. Overall, a favorable cost value of an N-of-1 trial compared with RCT is likely, but hinges on the complexity of the selected end points and scale of the comparator RCT (Table 2).

A limitation of the N-of-1 trial in PAH is the potential rapid nature of disease progression and the perils of drug withdrawal. Indeed, N-of-1 trials may be suited better for chronic, progressive diseases characterized by a predictable mortality, and event rate, as demonstrated in a recent N-of-1 analysis of statin therapy.56 Nevertheless, certain patients with PAH may warrant consideration for N-of-1 trial protocols when the disease pathophenotype is known to characterize individualized response to therapy. Consider these 3 patients with PAH, (1) a loss of function BMPR-2 mutation that promotes angioproliferative pulmonary vascular injury,57 (2) a loss of function KCNK3 mutation that impairs potassium channel function to promote pulmonary vascular dysfunction,21 or (3) pulmonary vascular inflammation and fibrosis in the setting of scleroderma-associated PAH. Despite an overlapping histopathology between these 3 patients, interchangeability of directed therapy to restore BMPR-2–dependent signaling is unlikely to abrogate pulmonary hypertension in the latter 2 patients, and vice versa for drugs that target pulmonary vascular inflammation to treat scleroderma-associated PAH in the first 2 cases. Therefore, a trial of individualized therapy in an N-of-1 setting may play a role in these patients.

The N-of-1 clinical trial design is well-positioned to identify therapies that are beneficial for specific PAH subpathophenotypes, but it is unlikely to lend insight to the management of patients with PAH broadly, which is where investigational end points play a role (ie, by correlating the clinical improvements with changes in novel markers of disease).58 A thorough discussion of the various statistical methods used to analyze data from N-of-1 trials is reviewed by Lillie and colleagues.59
Limitations of Novel Trials in PAH

There are important characteristics of PAH that may influence use or success of novel trial designs. PAH is a progressive disease with a variable clinical trajectory, which may confound drug efficacy within a single patient to generate both false-positive and false-negative results. Along these lines, because currently available therapies for PAH have not been shown to reverse disease pathobiology, the assessment of drug efficacy within a patient across different clinical stages of PAH is challenging. Thus, the timing of PAH-specific therapy initiation, which is controversial among experts, is unlikely to be resolved by these alternative trial designs. In addition, drug withdrawal is associated with acute clinical worsening in some patients with PAH, and, therefore, RDTs, withdrawal studies, and N-of-1 trial planning should be well within the framework of expert consensus guidelines for good clinical practice in PAH, including access to expert PAH care providers and specialized clinical PAH systems.60

Conclusions

PAH is a rare and heterogeneous disease characterized by elevated rates of mortality and heart failure–associated morbidity. Variability in PAH pathophenotype is a likely contributing factor to difficulty generalizing RCT findings to patients in clinical practice.43 By contrast, we think that crossover, RDT, and N-of-1 study designs are well positioned to study outcomes in selected patient cohorts with PAH defined by converging genetic or molecular PAH pathophenotypes and provide hypothesis-generating data for future study in large RCTs (Table 1). We anticipate that achieving individualized treatment strategies in PAH ultimately hinges on the application of the novel clinical trial strategies discussed. Furthermore, we think that these strategies are necessary for developing cost–effective methods that identify patients with PAH likely to benefit from disease-specific pharmacotherapies.

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