Evaluating Recent Therapeutic Trials in Pulmonary Arterial Hypertension: Raising the Bar for Clinical Investigation

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In the decade or more since epoprostenol became available, tremendous progress has been made in the treatment of pulmonary arterial hypertension (PAH). Groundbreaking laboratory discoveries partnered with robust drug development have transformed what was once a highly lethal disease with little hope for improvement into a chronic manageable condition for many patients. Specifically, 7 new therapies have been approved for the treatment of PAH in the United States since 1995, including one within the last few months. This current roster of therapies modulates 1 of 3 key pathways implicated in the pathogenesis of PAH—endothelin-1, nitric oxide, or prostacyclin.[1]

Recently, several important clinical investigations have finished, providing some important new information but also underlining challenges in designing therapeutic trials in the area. This article will first present the limitations of the 6-minute walk (6MW) test as a primary endpoint in therapeutic trials; next recent selected therapeutic trials will be examined which include both monotherapy and combination therapy designs. Finally, the future of PAH trials will be introduced, including the potential of morbidity/mortality trials as a more rigorous means to establish future therapeutic agents and treatment strategies.

6MW Test as a Primary Endpoint

Many well-done therapeutic trials have been completed in PAH during the last decade.[2] The design of these modern placebo-controlled, double-blind, randomized investigations has been remarkably similar in terms of the cohorts assembled, duration of blinded treatment, and endpoints assessed. These investigations have been short-term studies (ie, 12-18 weeks) utilizing a measure of sub-maximal exercise capacity, the 6MW distance, as the primary endpoint.

The 6MW test has become integral to clinical practice and clinical investigation in PAH. Because impaired exercise capacity is the hallmark clinical feature of PAH, some measure of exercise capacity has been an important endpoint of therapeutic trials. The 6MW test is a simple, widely used, and reproducible study requiring minimal equipment; the results correlate with other measures of exercise capacity[3] as well with the New York Heart Association functional classification, a frequently used measure of a patient's functional status and overall well-being.[5] As a sub-maximal exercise test, the 6MW protocol also mirrors activities of daily living more closely than other exercise protocols.[4] With attention to a few details, as outlined by the American Thoracic Society, the 6MW test provides a valid and reproducible measure of exercise capacity that can be sensitive to interventions, including pharmacotherapy.[6]

While "harder" endpoints such as death, hospitalization, or transplantation are more clinically meaningful, they have significant limitations as primary endpoints for PAH trials. The low background rate of these events makes it difficult even for an effective investigational agent to show significant benefit over placebo in a short-term trial. Fortunately the short-term event rate is even lower for patients enrolling in recent clinical trials, as they enjoy some protection from clinical deterioration thanks to approved, PAH-specific drugs both as baseline therapies and as rescue agents in deteriorating patients. These factors, however, add to the challenge of designing a safe but scientifically rigorous trial in small PAH patient populations. Therefore, the 6MW test has become a surrogate endpoint in most PAH trials, based on its ease of administration and ability to predict long-term outcomes.[5, 8] Continued use of the 6MW test has also been sustained by regulatory authorities, who have accepted the measure as a valid surrogate endpoint when judging the clinical merit of investigational agents.[9]

Despite its critical role in pivotal trials during the last 10 years, there are shortcomings of the 6MW test that become apparent when analyzing contemporary trials. The test is influenced by many confounding and immutable variables, including age, gender, stride length, and co-morbid conditions that affect exercise performance. In particular, advancing age and greater number of co-morbid conditions have become more relevant issues as study populations have diversified. There is also limited information on normal values for the 6MW test; existing prediction equations only account for ~40% between-subject variance.[10, 11] Finally, the issue of "minimally significant" improvement in the 6MW distance remains unresolved, especially as the magnitude of the post-intervention improvement diminishes in clinical trials. As a frame of reference, the coefficient of variation of the 6MW distance in patients with chronic obstructive pulmonary disease is estimated to be 8%.[6] If we assume the same is true for PAH patients, then a

Key Words—clinical trial design, clinical trial endpoints, combination therapy, pulmonary hypertension
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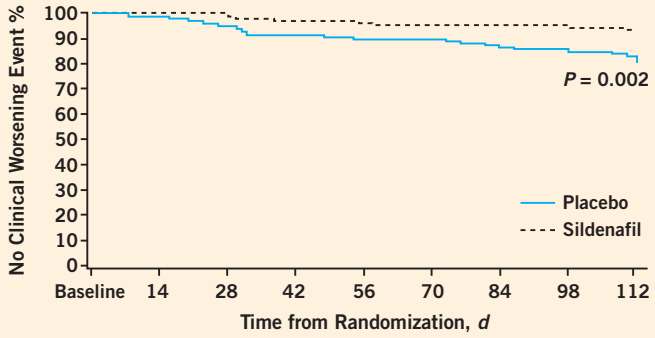

Treatment	Persons at risk (Censored), *n*				
	Baseline	Day 28*	Day 56†	Day 84‡	Day 112§
Epoprostenol + placebo	131	123 (1)	116 (0)	111 (2)	70 (36)
Epoprostenol + sildenafil	134	134 (0)	128 (2)	125 (2)	78 (44)

Figure 1. Time to clinical worsening from the PACES study. Reprinted with permission from Simonneau G, et al.[25]

tion. Customary side effects associated with prostanoids (eg, headaches, dyspepsia, extremity pain, diarrhea) were more frequent in the sildenafil group, suggesting that sildenafil potentiated prostacyclin-associated side effects.

In summary, the aggregate results of the PACES investigation confirm the benefit of adding *high-dose* sildenafil to epoprostenol in patients that remain significantly impaired. But these benefits have to be considered in light of the potential limitation that some patients may not have been fully optimized on epoprostenol at the time of enrollment. More importantly, it's critical to remember that the study utilized 80 mg TID of sildenafil, a dose higher than the currently approved dose, and one that is unattainable for many patients due to insurance barriers.

The PACES trial is noteworthy on many levels. First, it underscores the challenge of conducting clinical trials with parenteral prostanoids because of the variability and uncertainty over optimal prostacyclin dosing. Second, the improvement in 6MW distance is somewhat disconnected from the hemodynamic and survival benefit enjoyed by sildenafil-treated patients, especially for the group with the worst baseline 6MW distance. Given its much larger size than other combination therapy trials (eg, 4x enrollment of the STEP trial), the PACES study still had enough statistical power to demonstrate a statistically significant difference in the 6MW distance, even though the magnitude of improvement is smaller than the pivotal monotherapy trials and similar to the statistically insignificant 6MW distance improvement seen in the STEP trial. Finally, PACES measured a reduction in clinical worsening despite less impressive improvements in a standard measure of exercise capacity, which again underscores the notion that the 6MW test may be insensitive to important benefits of combination therapy.

Inhaled Treprostinil and Oral Therapy (TRIUMPH)

The TRIUMPH study evaluated substantial numbers of patients receiving baseline oral endothelin antagonists or phosphodiesterase inhibitors, yet remained in New York Heart Association functional class III or IV. The results have been presented at an international scientific meeting.[27] Two-hundred and thirty-five PAH patients inhaled treprostinil (up to 56 micrograms/treatment) or placebo 4 times a day.[27] After 12 weeks and at times of peak study drug levels, the median placebo-adjusted 6MW distance was 20 meters more for the treprostinil group, which was statistically significant. The magnitude of improvement was more impressive in the quartile of patients with lowest baseline 6MW distances. Other measures of efficacy, including functional classification and clinical worsening did not differ significantly between the 2 groups.

Tadalafil and Bosentan

As mentioned earlier, just over half of the patients enrolled (216/405) in the PHIRST trial (tadalafil vs placebo) were already taking bosentan at study enrollment. While the overall results of PHIRST are encouraging, it is clear that the magnitude of improvement in the placebo-adjusted 6MW distance was less in the combination therapy group (ie, bosentan + tadalafil) than with the treatment-naïve group.[12] The PHIRST investigation further strengthens the notion that more modest 6MW improvements may be expected in combination therapy trials.

These completed combination therapy studies consistently demonstrate smaller gains using the traditional 6MW distance when studying patients already stabilized on PAH-specific therapies, suggesting that additional measures, such as hemodynamics, well-defined clinical events, measures of RV function, or novel endpoints need to be considered as the next wave of therapies is investigated.

Future Clinical Investigations

As study populations have shifted from treatment-naïve patients with advanced symptoms to less symptomatic subjects already on PAH-specific agents, smaller improvements are anticipated during short-term studies involving 3-4 months of blinded investigation. To identify improvements that might only be observed over a longer period of time, the EARLY trial of bosentan vs placebo in mildly symptomatic (functional class II) patients compared outcomes at 6 months. The investigators noted significant reduction in the primary endpoint of pulmonary vascular resistance and improvement in a key secondary endpoint of time to clinical worsening.[29] In addition, the ongoing ATHENA-1 investigation (ambrisentan + sildenafil vs placebo + sildenafil [www.clinicaltrials. gov]) has been designed to assess its primary endpoint (change in pulmonary vascular resistance) 6 months after randomization. Finally, open-ended, event-driven studies are also being conducted (see below).

Even with longer duration trials, future reliance on the 6MW distance as the primary endpoint of investigation is in doubt, especially for combination therapy studies. The magnitude of placebo-corrected change in 6MW distance in the completed combination trials is clearly smaller. This reduction in the treatment effect size may be related to: 1) stability of placebo patients, 2) failure of combination therapy to improve sub-maximal exercise capacity, 3) a ceiling effect of the 6MW test,[30] or 4) perhaps other factors (eg, deconditioning, arthritis or skeletal muscle dysfunction) that become unmasked once exertional dyspnea lessens. Furthermore, the effect of higher baseline 6MW distances (in some trials) coupled with smaller treatment effects have led to smaller relative increases in the 6MW distance; some would question the clinical relevance of such modest relative improvements in exercise tolerance.

As limitations of the 6MW are surfacing, greater attention is being focused on the composite clinical endpoint of time to clinical worsening, which can also be depicted as "event-free" sur-

Table 3. Novel therapeutic candidates for future clinical trials.

Soluble cyclic GMP Agonist
Nitric Oxide Synthase Coupler
Tyrosine Kinase Inhibitors
Endothelial Progenitor Cell Transplantation
(Editor's note: the above agents are covered in Dr. Langleben's accompanying article)
Tissue-tropic Endothelial Receptor Antagonist
Prostacyclin Receptor Agonist
Rho A Kinase Inhibitor
Statins
Serotonin Receptor Antagonists
Serotonin Transporter Inhibitors

vival.[20] Composite endpoints have greater clinical relevance than a simple measure of exercise capacity and are often used in other areas of clinical research, including acute myocardial infarction, cancer, and sepsis. While a consensus definition of clinical worsening in PAH has not been established, key elements have consistently included death, hospitalization, transplantation, addition of a prostanoid, or clinical decline defined as a mix of worsening symptoms/signs, declining objective measure, and a therapeutic intervention that is typically the addition of PAH-specific therapy.

Morbidity/Mortality Investigations

With these recent trends, a warning bell has been sounded to redefine treatment goals.[31, 32] A working group, assembled as part of the 4th World Pulmonary Hypertension Symposium (Dana Point, California, February 2008), endorsed the notion of longer-term, morbidity/mortality investigations in PAH with greater reliance on time to clinical worsening as the primary endpoint in future investigations.

Morbidity/mortality investigations are already in progress, but pose unique challenges with respect to subject enrollment and retention. The first morbidity/mortality trial in PAH is the COMPASS-2 investigation, which is still enrolling subjects already taking sildenafil for 12 weeks and adding either bosentan or placebo [www.clinicaltrials.gov]. Its objective is to determine whether patients on the combination of sildenafil and bosentan will experience a delay in time to first adjudicated morbidity/mortality event, as compared to patients on sildenafil (and placebo). A formidable challenge with this type of event-driven, morbidity/mortality trial is the duration of blinded investigation, especially when the background clinical event rate is lower than anticipated. COMPASS-2 has been open since early 2006 and is not anticipated to finish until 2011. Such a lengthy trial underscores the difficulty of conducting a large-scale clinical trial on a landscape of evolving therapeutic options. Another similarly designed morbidity/mortality trial (SERPAHIN), launched in 2008, is investigating the clinical efficacy of a new endothelin receptor antagonist with unique biochemical properties; recruitment is going well in several countries [www.clinicaltrials.gov]. Even though morbidity/mortality trials are challenging to design and grueling to complete, they provide a higher level of rigor in evaluating new treatment strategies and should be encouraged, especially for combination therapy studies.

As the next generation of pharmacologic agents reaches clinical investigation, the recommendations of the 4th World Pulmonary Hypertension Symposium for longer-term investigations with (primary) morbidity/mortality endpoints should be adopted. A partial list of investigational agents is listed in Table 3. Some of these agents modulate new pathways and may affect cellular proliferation, a key aspect of the vasculopathy that is the hallmark of the disease. To provide the best opportunity for these new agents to have meaningful impact *above-and-beyond current therapies*, combination therapy trials must be large enough to have adequate power, lengthy enough to allow for the required number of events to occur, and utilize meaningful clinical endpoints of study.

Conclusion

Relying heavily upon the 6MW test, investigations in PAH have brought numerous therapies to clinical practice. By themselves, these therapies lead to well defined short-term benefits, but most are still inadequate in terms of longer-term disease control. To meet this more challenging need, new therapeutic agents and treatment strategies will be forthcoming to judge these new interventions fairly and to apply them appropriately to the current therapeutic landscape, clinical investigation in PAH will also need to evolve beyond the present mode.

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