Ask the Expert: A Regulatory Perspective on Clinical Trials for Pulmonary Arterial Hypertension

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Norman Stockbridge, MD, PhD Center for Drug Evaluation and Research US Food and Drug Administration Silver Spring, MD Pulmonary arterial hypertension (PAH) is a rare, progressive disease. There are 11 drugs available in the United States to treat adult PAH patients; however, all drugs primarily act through vasodilation and have modest effects on clinical endpoints. None of these drugs can claim survival benefit in their product labels. New drugs are needed that target other mechanisms in the disease to have durable benefits for patients. To demonstrate clinical benefit, new drugs are now tested in large, randomized, placebo-controlled trials evaluating their effect to delay clinical worsening, a composite endpoint of morbidity events and death. Efficient clinical trial designs, such as the use of enrichment strategies, that reduce the number of patients and trial duration would be valuable for this disease. It would also be desirable to have new clinical endpoints that measure improvement in quality of life and allow the use of extrapolation strategies to the pediatric population. Academic, industry, and regulatory partnerships are key to advancing therapies for this disease.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is still considered a rare disease for drug development. The Orphan Drug Act (ODA) defines a rare disease as one affecting fewer than 200000 in the United States.¹ Although the prevalence of PAH is estimated to be around 10 per million in the United States, pulmonary hypertension was given orphan disease status in 1985 when the prevalence of the disease was thought to be <200 000.²⁻⁴ The ODA gives pharmaceutical companies financial incentives to develop drugs to treat rare diseases affecting a limited patient population.⁵ The ODA does not, however, relax the criteria for "substantial evidence" needed to demonstrate that the drug is effective in treating a disease. For PAH, evidence of effectiveness has usually been satisfied by a single multicenter, randomized, placebo-controlled clinical trial demonstrating clinical benefit, supported by other studies showing hemodynamic

improvement or clinical benefit in other pulmonary hypertension groups. The Food and Drug Administration (FDA) approved the first PAH-specific therapy (epoprostenol) in 1995 and has subsequently approved 10 additional new drugs over the past 2 decades. Most drugs have demonstrated clinical benefit by improving the 6-minute walk distance or, more recently, by decreasing the occurrence of clinical worsening. Although none of these drugs can claim survival benefit in their product labels, survival in patients followed in PAH registries has improved since the availability of these therapies.^{4,6} The 5-year survival is 61% compared with 34% in the 1980s.^{6,7} Besides the availability of PAH-specific therapies, other possible reasons for the improved survival are lead-time bias due to better awareness of PAH, better clinical management of right ventricular failure, and better outcomes in patients receiving heart-lung transplants.^{4,6} Despite the significant

progress in treating patients with this rare disease, drug development challenges remain, such as finding drug mechanisms other than vasodilation, improving the efficiency of clinical trials that use time to clinical worsening as their primary endpoint, developing endpoints that reflect benefits in patient symptoms and quality of life, and expanding the number of drugs available to pediatric patients with PAH.

DRUGS TARGETING OTHER MECHANISMS

Patients with PAH exhibit enhanced pulmonary arteriolar contractility, endothelial dysfunction, remodeling and proliferation of endothelial and smooth muscle cells, and thrombosis.8 The outcome of these physiological changes is partial occlusion of the small pulmonary arteries leading to increased pulmonary vascular resistance (PVR), right heart failure, and death. All approved drugs primarily act through vasodilation, which, considering how small the drug effects are, must be a minor component of the disease. These drugs target 3 key signaling pathways in smooth muscle cells: prostacyclin, nitric oxide, and endothelin (ET) pathways.⁹ Prostacyclin analogues (epoprostenol, treprostinil, ilo-

Key Words—pulmonary arterial hypertension, clinical trials, enrichment strategies, pediatrics, patient-reported outcomes

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prost) and receptor agonists (selexipag) increase cyclic adenosine monophosphate concentrations in smooth muscle cells and cause pulmonary vasodilation. The phosphodiesterase-5 inhibitors (sildenafil, tadenafil) and guanylate cyclase stimulators (riociguat) augment nitric oxide-cyclic guanosine monophosphate pathways and promote the vasodilatory and antiproliferative effects of nitric oxide. ET receptor antagonists, which are available as selective for ET_A (ambrisentan) or nonselective for ET_A and ET_{R} receptors (bosentan, macitentan), decrease ET concentrations and promote relaxation and reduced proliferation of smooth muscle cells. The main disadvantage of the currently available agents is that none directly target the adverse vascular remodeling in the pulmonary vasculature, and most do not improve right ventricular function. New drugs are needed that target other mechanisms in the pathophysiology, such as immune dysfunction, vascular cell proliferation, and right ventricular dysfunction.⁴

Drugs that target vasoconstriction have only modest effects on efficacy endpoints. In Phase 3 trials, most drugs have small increases in 6-minute walk distance (average of +30 m), an improvement (relative to placebo) of only about 10% from baseline and small compared with the day-to-day intrapatient variability. Such improvement may not be easily perceived by patients. Selexipag and macitentan showed 40%–45% reduction in the occurrence of clinical worsening, a composite endpoint of death, hospitalization, and other measures of disease progression, but the benefit was attributed to a reduction in hospitalizations for PAH worsening or other disease progression events.^{10,11} Oral treprostinil showed 25% reduction in the occurrence of clinical worsening, which was attributable to a reduction in disease progression events, but not with the other components of the endpoint.¹² Administering a combination of ambrisentan and tadalafil reduced the occurrence of clinical failure by 50% compared to pooled monotherapy in treatment-naïve patients at high risk.¹³ None of the drugs tested in large, event-driven trials have demonstrated an improvement in survival.

EFFICIENT CLINICAL TRIAL DESIGNS

Clinical trial designs testing new therapies are now large, placebo-controlled, event-driven trials assessing time to clinical worsening in PAH patients receiving background treatment. Patients need to be followed for 3-5 years to achieve the target number of events for statistical power. One approach to improve the efficiency of these trials is to use enrichment strategies.¹⁴ Prognostic enrichment uses patient characteristics to select a higher-risk study population in which detection of a drug effect is more likely than in an unselected population. Prognostic enrichment does not affect the relative risk reduction but increases the event rate, reducing overall sample size requirements. A recent proof-of-concept study demonstrated the feasibility of using the COMPERA,¹⁵ the French score,¹⁶ or REVEAL¹⁷ risk scales to identify PAH patients who are more likely to experience a clinical worsening event for trial enrichment.¹⁸ When these risk scores were applied retrospectively to the Griphon,¹¹ Ambition,¹³ and Seraphin¹⁰ clinical trials, patient enrichment strategies reduced needed enrollment size and the duration of treatment and observation. An enrichment strategy has many significant patient benefits, such as reducing the duration of treatment with placebo and improving time-to-market for potentially lifesaving medications. The FDA has no reservations about bridging treatment efficacy to lower risk groups because the current understanding of the PAH disease state and pathophysiology supports a treatment effect regardless of a patient's individual risk of morbidity or mortality at baseline.

ENDPOINTS THAT REFLECT PATIENT IMPROVEMENT

Primary efficacy endpoints in pivotal PAH trials have been focused on measurements of exercise function (eg, 6-minute walk distance) or assessments of clinical events (eg, composite of morbidity events and death), but have not focused on measures of patient symptoms and how the symptoms impact quality of life. It is desirable to have a

patient-reported outcome (PRO) instrument that measures treatment benefit in patients' symptoms as secondary endpoints in clinical trials. Commonly used quality-of-life measures in PAH trials include the 36-item Medical Outcomes Study Short Form Survey (SF-36 v2)¹⁹ or the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)²⁰ questionnaire, but none of these measures has been used to support a labeling claim. Recently, the Pulmonary Arterial Hypertension-Symptoms and Impact Questionnaire (PAH-SYMPACT) instrument for quantifying PAH symptoms was developed and evaluated as a PRO instrument for PAH patients.²¹ The questionnaire measures important, patient-relevant aspects of PAH symptoms and impacts of the symptoms that are not captured by other clinical endpoints. PRO instruments can support a labeling claim; interactions with FDA's Clinical Outcomes Assessment (COA) Staff can assist in developing instruments with a good chance of successfully demonstrating drug effects.²² The FDA lists information about submissions to the COA Qualification Program, including FDA's decision to accept or not accept the submission.²³

PREDICTIVE BIOMARKERS AND SURROGATE ENDPOINTS

PAH is a disease that lacks validated surrogate endpoints appropriate for approval. A surrogate endpoint is expected to predict clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence and is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives.²⁴ The FDA has used PVR as a surrogate endpoint under specific scenarios for drugs that have been approved for the treatment of PAH. The FDA evaluated the relationship between change from baseline in PVR and 6-minute walk distance using pooled patient-level data from 2028 adults with PAH in controlled, clinical trials.²⁵ The estimated slope $[0.055 \text{ m/dyne} \cdot \text{s/cm}^5 (95\% \text{ CI} =$ 0.62, 0.047)] was consistent in magnitude across 4 drug classes and 9 individual drugs. The FDA used the relationship to extrapolate the efficacy from

adults to children using PVR to approve bosentan in pediatric PAH patients, where PVR was determined during right heart catheterization.²⁶ This approach cannot be used for other drugs because of the view that right heart catheterization poses more than minimal risk for pediatric patients; therefore, assessment of PVR as obtained through the use of right heart catheterization is no longer considered appropriate in pediatric trials.²⁷ In adults, PVR has been used as a primary endpoint in clinical trials testing the efficacy of combination therapy of 2 PAH drugs and to assess whether a new therapy has a sustained effect on PVR after the drug was discontinued. As drugs targeting new pathophysiology processes in PAH enter clinical development, the endpoints should be tailored to the disease biology and anticipated mechanistic effects, thereby allowing for potential regulatory consideration of novel biomarkers.²⁸

DRUGS TO TREAT PEDIATRIC PAH

Although 11 drugs have been approved in the United States for the treatment of PAH in adults, to date only bosentan has been approved for the treatment of PAH in children. The FDA's approach using PVR as a surrogate endpoint to bridge dose response with clinical efficacy cannot be generalized to other drugs because the routine use of serial right heart catheterizations in clinical trials is now considered unethical in children. There is widespread recognition that treatments are needed for children with PAH, but it has been difficult to conduct trials in this population.²⁹ One reason that has been cited is the lack of clinical equipoise once a new treatment is approved for adults and used extensively off label in children. Moreover, clinical practice guidelines for pediatric PAH recommend similar treatment strategies that are used in adults despite the lack of randomized clinical trials of the same therapies in children.³⁰ Another challenge has been identifying feasible and reliable endpoints for demonstrating efficacy in children. The 6-minute walk test has been used in most drug development programs to establish the efficacy of new therapies for PAH in adults. The

6-minute walk test is not appropriate for all children with PAH for reasons of reliability in young children (less than 6 years) and those with developmental impairment.^{27,31} Clinical trials using time to clinical worsening endpoints may not be feasible in pediatric trials because they generally require large trials and long duration of follow-up to observe events. Extrapolating the effectiveness of approved PAH treatments for adults to the pediatric population will require the development of noninvasive predictive biomarkers that are as robust as PVR. Therefore, novel approaches to both trial design and endpoints are needed to evaluate the efficacy and safety of PAH treatments in children. The FDA is open to discussing alternative pathways, novel endpoints, and novel trial designs with sponsors who are developing treatments for pediatric patients with PAH.

CONCLUSION

Although the FDA will still approve nonspecific vasodilators for PAH, and such drugs remain in development, particularly for less well-studied forms of PAH, the era of the nonspecific vasodilator is ending. Antiproliferative therapy seems likely to have the potential to achieve larger, more durable benefits.

The FDA applied a fairly low standard for approval based on improvements in exercise capacity that were likely too small to be considered clearly clinically relevant. This, too, is changing, and more recent approvals have incorporated a clinical worsening endpoint for which there is no lower bound for clinical relevance.

Academic, industry, and regulatory partnerships are key to making the best use of available data to inform efficient trial design for new drugs in adults and to bridge existing therapy to pediatric populations.

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