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The Role of Biomarkers and Surrogate End Points in Drug Development for Neonatal Pulmonary Arterial Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a rare disease in newborns, infants, and children. It is associated with significant morbidity and mortality, but has limited treatment options. Except for inhaled nitric oxide, which is approved for persistent pulmonary hypertension of the newborn (PPHN), no drug is approved for the treatment of newborns, infants, and children with PAH. The lack of developmentally appropriate pediatric efficacy end points and pediatric clinical trials contribute to this unmet medical need. The noninvasive biomarkers reported in the literature that can be used as potential surrogate end points to assess disease severity and treatment response in neonates, infants, and children with PAH are reviewed herein. In addition, the role of the US Food and Drug Administration in developing potential biomarkers as surrogate end points to facilitate drug development for the treatment of children with PPHN and PAH in children is reviewed herein.

INTRODUCTION

Typically, pulmonary hypertension is a normal and necessary state for the fetus because the fetus relies on the placenta, rather than the lungs, as the organ of gas exchange. In fetal circulation, only 5% to 15% of the combined ventricular output is directed to the pulmonary vascular bed. This is because most of the right ventricular (RV) output crosses the ductus arteriosus to the aorta. Even though the pulmonary vascular surface area increases with fetal lung growth, pulmonary vascular resistance (PVR) increases with gestational age when corrections are made for lung or body weight, suggesting that pulmonary vascular tone increases during late gestation. (1) As a result, in utero pulmonary pressures are equivalent to systemic pressures because of elevated PVR. A dramatic cardiopulmonary transition occurs at birth to facilitate the transition to gas exchange by the lungs. This is characterized by a rapid fall in PVR and pulmonary artery pressure and a 10-fold rise in pulmonary blood

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Note: The views expressed in this article are those of the authors and do not necessarily reflect official positions or policies of the FDA.

flow. (1) Shortly after birth, right atrial pressure is close to zero in neonates. (2) Eventually, the mean pulmonary arterial pressure reaches a normal range of 8 to 25 mm Hg within 2 months after birth. (3)(4) Severe persistent pulmonary hypertension of the newborn (PPHN) is a result of failure of the normal cardiopulmonary transition. (1)

Pulmonary arterial hypertension (PAH) is defined as the presence of abnormally high pulmonary artery pressure with specified parameters of a mean pulmonary artery pressure of 25 mm Hg or more at rest, or 30 mm Hg or more during exercise, and a normal capillary wedge pressure of 15 mm Hg or less. The definition of PAH in children is the same as that in adults. Similar to adults, PVR is excluded from the definition of pediatric PAH. (4) The minimum value corresponding to an increased PVR remains controversial, especially in pediatric patients. In children, PAH caused by left-to-right congenital shunt is common, and in such cases, no significant increase in PVR is observed. (5)(6) PAH can occur at any age from newborns to adults. PPHN is a form of PAH that is estimated to occur in 0.2% of liveborn term infants. (1) Some degree of PAH complicates the course of more than 10% of all neonates with respiratory failure. (1) Currently, only inhaled nitric oxide has been approved for PPHN in term or near-term neonates. No drugs have been approved for the treatment of PAH in children. The lack of suitable efficacy end points and clinical trials in the pediatric population with PAH has contributed in part to this unmet medical need.

Previous reviews have discussed the general use of biomarkers in adults with PAH, (7)(8)(9) whereas others have focused on the specific areas of the noninvasive biomarkers used in PAH. (10)(11) For example, Cracowski and Leuchte emphasized the prognostic value of biomarkers that are associated with the pathophysiologic process of PAH, including endothelial dysfunction, RV failure, inflammation, and oxidative stress. (11) Recently, Colvin et al conducted a review to explore the current state of noninvasive biomarkers studied in adults with PAH that potentially could be used to guide the accurate diagnosis, treatment, and prognosis of this disease in children. (5) The objective of our review is to define the role of biomarkers in developing drugs for neonates, infants, and children with PAH. We also explain how biomarkers might serve as surrogate end points to assess treatment benefit, disease progression, and long-term safety signals. It is also important to recognize that the physiologic developmental changes in the pediatric population must be considered when using biomarkers in clinical trials to support the evaluation and approval of new therapies. In addition, we describe the role of the US Food and Drug Administration (FDA) in the development of potential biomarkers as surrogate end points to facilitate drug development for the treatment of PPHN and PAH in children.

DEFINITIONS OF BIOMARKERS AND SURROGATE END POINTS

The National Institutes of Health Biomarker Definition Working Group defines the biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention”.(12) A biomarker can be a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biologic function or process. Biomarkers measured in patients before treatment can be used to select patients for inclusion in a clinical trial. Biomarker changes after treatment may predict or

identify safety problems related to a candidate drug, or reveal pharmacologic activity expected to predict an eventual benefit of treatment. Biomarkers can help reduce uncertainty in drug development and evaluation by providing quantifiable predictions about drug performance, and they can contribute to dose selection. (12) Composite biomarkers consist of several individual biomarkers in a stated algorithm. This algorithm reaches a single interpretive readout when a single biomarker fails to provide all the relevant information required for assessment. (11)(12)

According to the FDA guidance, biomarkers that can be used in drug development include diagnostic, prognostic, predictive, and pharmacodynamic biomarkers, as briefly described herein. A *diagnostic* biomarker is a disease characteristic that categorizes a person by the presence or absence of a specific physiologic or pathophysiologic state or disease (eg, blood pressure). A *prognostic* biomarker is a baseline characteristic that categorizes patients by the degree of risk for disease occurrence or progression of a specific aspect of a disease (eg, expression levels of prostate-specific antigen and carcinoembryonic antigen). A prognostic biomarker provides information about the natural history of the disorder in that particular patient in the absence of a therapeutic intervention. It can be used as an enrichment strategy to select patients likely to have clinical events of interest or to progress rapidly. A *predictive* biomarker is a baseline characteristic that categorizes patients by their likelihood of response to a particular treatment relative to no treatment (eg, expression levels of the estrogen receptor and progesterone receptor in patients with breast cancer). A predictive biomarker can be used as an enrichment strategy to identify a subpopulation likely to respond to a treatment intervention in a particular way. It may predict a favorable response or an unfavorable response (ie, adverse event). A *pharmacodynamic* (or activity) biomarker is one for which a change in the biomarker shows that a biological response has occurred in a patient who has received a therapeutic intervention and for which the magnitude of the change is considered pertinent to the response. A pharmacodynamic biomarker may be treatment-specific or more broadly informative of disease response (eg, blood pressure and cholesterol). (12) Most pharmacodynamic biomarkers are used to guide drug development and usually not to obtain regulatory approval. (12)

A surrogate end point is a biomarker that is intended to substitute for a clinical end point and is expected, based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence, to predict clinical benefit. Surrogate end points can be a subset of pharmacodynamic biomarkers. Although all surrogate end points generally can be considered biomarkers, it is likely that only a few biomarkers would be appropriate for use as surrogate end points. (13) Typically, after extensive experience, sufficient knowledge of a particular clinical disorder and the biomarker's role in the disorder may accumulate to allow a few of these biomarkers to be used as surrogate end points (eg, blood pressure, low-density lipoprotein cholesterol, hemoglobin A1c).

CURRENT LITERATURE REVIEW OF NONINVASIVE BIOMARKERS USED IN PULMONARY ARTERIAL HYPERTENSION

We searched the electronic database PubMed/Medline using the phrase “PAH/AND biomarkers/AND disease severity or treatment response.” No language and time restrictions were applied during the search. The last search was conducted on November 1, 2014.

Of 326 retrieved biomarker publications relevant to PAH, we reviewed 88 related to disease severity and treatment response. The noninvasive measures, flow imaging modalities (magnetic resonance imaging [MRI], positron emission tomography [PET], Doppler), electrical velocimetry (EV), and dozens of circulating biomarkers, were studied to explore the possibility of serving as surrogate end points in adults with PAH. None of these parameters has been well-studied in neonates to assess disease severity and treatment response.

Typically PAH is defined by right heart catheterization, in which mean pulmonary artery pressure, cardiac output, and PVR measurements can be obtained. (14) However, echocardiography is the most important noninvasive tool used to detect and monitor the progression of PAH. (15) Echocardiographic findings, though subject to significant operator variability, (16) reliably provide several estimates of hemodynamic function that closely correlate with measurements obtained with right heart catheterization. A large variety of RV function estimates can be made, depending on assumptions of RV geometry. Flattening and inversion of the interventricular septum toward the left ventricle is highly suggestive of PAH. (5) Furthermore, technological advances have led to new techniques for evaluating RV function (3-dimensional echocardiography, strain, and strain rate) using echocardiography; however, more data are needed in the pediatric population to determine the reproducibility of these new techniques. (15) In addition, tissue Doppler imaging has been used to predict adverse outcomes in children with idiopathic PAH. (17) This approach measures 3 waveforms that represent the cardiac cycle: systolic myocardial velocity, early diastolic myocardial relaxation velocity, and late diastolic myocardial velocity associated with atrial contraction. A prospective study compared 51 children with idiopathic PAH with 51 controls and found that tricuspid early diastolic myocardial relaxation velocity had higher correlation with plasma B-type natriuretic peptide (BNP) levels and hemodynamics than did tricuspid systolic myocardial velocity. These findings differed with those in adults, (18)(19)(20) but support the idea that biomarkers in adults with PH should be systematically and comparatively examined in children with PAH. As with nearly all studies of pediatric PAH, interpretation of the study is constrained by the relatively small sample size. (5) This factor may be addressed in future studies by developing clinical trial networks that include more participants.

In adult patients with PAH or animal models, MRI (n=33) and PET (n=1) have been conducted to assess right heart dysfunction and increased resistance of pulmonary circulation, the hallmarks of PAH. Compared with the traditional diagnostic imaging modalities, primarily echocardiography, invasive heart catheterization, and ventilation/perfusion scintigraphy, MRI has a good balance of high spatial, temporal, and contrast resolution, requires no radiation exposure, and is highly accurate and reproducible. MRI also

provides both anatomic and functional information about pulmonary hemodynamics. This makes it ideal for monitoring changes in RV parameters and pulmonary circulation in response to therapy. PET imaging would not be suitable for neonates and infants because of the increased radiation exposure.

Electrical velocimetry is a noninvasive method of continuous left cardiac output monitoring based on the measurement of thoracic electrical bioimpedance. It has been compared with invasive methods of cardiac output measurements, particularly thermodilution techniques, which have demonstrated correlations of 87% in animal models, 85% in stable postsurgical adult patients, and 80% in children with congenital heart defects. (21)(22)(23) EV has also been compared with echocardiography in healthy term newborns during the first 2 postnatal days. (24) Noori et al found that the true precision of EV was similar to that of echocardiography (31.6% vs 30%, respectively). (24)

Many potential circulating markers related to heart failure, inflammation, homeostasis, remodeling, and endothelial cell-smooth muscle cell interaction have been identified for assessing PAH disease severity and treatment response. More recently, other markers such as circulating microparticles, endothelial cells, and endothelial progenitor cells have also been identified for assessing PAH disease severity and treatment response. These circulating biomarkers currently lack specificity, standardization, and validation required to serve as a surrogate end point. Further studies are needed to demonstrate their potential use in neonates and infants with PAH. For example, N-terminal proBNP (NT-proBNP) is a biomarker of disease severity in PAH. It has been studied to determine if the baseline NT-proBNP levels correlate with improvement in “6-minute walk distance” (6MWD, a typical study end point to assess disease severity and treatment response in adult PAH trials) in a randomized, placebo-controlled, double-blind study adding inhaled treprostinil to oral therapy in 178 adults with PAH. (25) The authors of that study found that baseline NT-proBNP levels demonstrated a strong interaction with treatment in predicting change from baseline for 6MWD ($P < .01$). Patients with high levels of NT-proBNP at baseline showed greater improvement in 6MWD after treprostinil treatment. (25)

In summary, although echocardiography, MRI, PET, EV, and circulating NT-proBNP levels have shown some potential in both adults and children, none has been correlated with clinical end points or has the sensitivity of differential treatment effect required for surrogate end points to assess efficacy and long-term safety signals.

SURROGATE CRITERIA AND THE BIOMARKER QUALIFICATION PROGRAM AT THE FOOD AND DRUG ADMINISTRATION

The primary outcome measure in definitive trials should use clinically meaningful end points, which is either a clinical event relevant to the patient or an end point that directly measures how a patient feels, functions, or survives. (26) For example, 6MWD has been used and accepted as a primary clinically meaningful end point in about 90% of the adult PAH trials to support product approval. However, it would not be applicable in young children and neonates who would need an age and developmentally appropriate clinical end point to measure study outcomes and treatment benefit. Alternatively, an end point can be a

validated surrogate for an outcome measure such as improved physical and cardiorespiratory performance. Validating a surrogate end point requires providing rigorous scientific evidence and justification, often from randomized, controlled clinical trials. Such evidence must support the idea that the surrogate end point reliably predicts important changes in a clinically meaningful end point, regardless of the mechanism by which the surrogate is affected. (26)

A substantial risk exists of adversely affecting public health when a biomarker is not a valid surrogate but used to make drug use or approval decisions. Numerous biomarkers have represented plausible surrogate end points (eg, reduced rate of ventricular premature beats after a heart attack, cardiac output in congestive heart failure, increased high-density lipoprotein cholesterol in patients with coronary artery disease). However, when tested in outcome trials, these biomarkers have failed to predict the expected clinical benefit of improved cardiac function and health. A biomarker qualifies as a surrogate end point far less frequently than for other uses.

The Biomarker Qualification Program was established to support the FDA's work with external scientists and clinicians in developing biomarkers. As an interoffice collaborative endeavor within the FDA, the Biomarker Qualification Program offers a formal process to guide investigators as they develop biomarkers and seek evaluation for use in the regulatory process and approval of new therapies.

The goals of the FDA Biomarker Qualification Program are to: (1) provide a framework for scientific development and regulatory acceptance of biomarkers for use in drug development; (2) facilitate integration of qualified biomarkers in the regulatory review process; (3) encourage the identification of new and emerging biomarkers for evaluation and utilization in regulatory decision-making; and (4) support outreach to relevant external stakeholders to foster biomarker development.

However, a biomarker cannot become qualified without a reliable means to measure it. Therefore, the performance characteristics of the method used to provide the biomarker data need to be considered. In addition, qualification of a biomarker does not automatically imply that a specific test device used in the qualification process for a biomarker has been reviewed by the FDA and cleared or approved for use in patient care.

A biomarker may also have potential value outside the boundaries of the qualified context of use. As data from additional studies are obtained over time, submitters of biomarkers will be able to continue to work with the Biomarker Qualification Program to submit additional data and expand the qualified context of use.

DISCUSSION

The discovery and validation of appropriate noninvasive biomarkers would be helpful for PAH trials in neonates, infants, and children. Although some existing noninvasive biomarkers have shown potential to be developed as surrogate efficacy end points, these would need to be validated and standardized to demonstrate specificity and reliability required. It needs to be pointed out that biomarkers in children with PAH are likely to be

more differentially influenced by degree of physical activity, age in years and/or stage of development, gender differences, and nutritional status, compared with biomarkers for adults. (5)

To make progress in drug development, validated biomarkers serving as surrogate end points would be helpful for PAH trials in neonates, infants, and children. The FDA seeks scientific input and collaboration among academia, industry, government, and families. Such collaborations can help develop, validate, and qualify age and developmentally appropriate and possibly more efficient efficacy end points in drug development for neonates, infants, and children with PAH.

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Objectives

After completing this article, readers should be able to:

1. Define the role of biomarkers in drug development for neonates, infants, and children with pulmonary arterial hypertension.
2. Explain how these noninvasive biomarkers might serve as surrogate end points to assess treatment benefit, disease progression, and long-term safety signals.
3. Recognize that the evaluation and approval of new therapies must incorporate biomarkers that account for the physiologic developmental changes in the pediatric population.

American Board of Pediatrics Neonatal–Perinatal Content Specifications

- Understand the factors affecting and regulating the pulmonary circulation in the fetus and newborn infant and during the transitional period.
- Recognize the laboratory, imaging, and other diagnostic features of persistent pulmonary hypertension.
- Know the management of persistent pulmonary hypertension including assisted ventilation, pharmacologic approaches, and ECMO.