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Reliable and developmentally appropriate study end points are needed to achieve drug development for treatment of pediatric pulmonary arterial hypertension

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Abstract

OBJECTIVE—To identify suitable end points and surrogates for pediatric pulmonary arterial hypertension (PAH) as the lack of developmentally appropriate end point and clinical trials contribute to the unmet medical need.

STUDY DESIGN—Reviewed the efficacy end points and surrogates for all trials (1995 to 2013) that were submitted to the Food and Drug Administration (FDA) to support the approval of PAH therapy and conducted literature search.

RESULTS—An increase in the 6 min walking distance (6MWD) was used as a primary end point in 8/9 adult PAH trials. This end point is not suitable for infants and young children because of performance limitations and lack of control data. One adult PAH trial used time to the first morbidity or mortality event as a primary end point, which could potentially be used in pediatric PAH trials. In the sildenafil pediatric PAH trial, the change in pulmonary vascular resistance index or mean pulmonary artery pressure was used as a surrogate for the 6MWD to assess exercise capacity. However, two deaths and three severe adverse events during the catheterizations made this an unacceptably high-risk surrogate. The INOmax persistent pulmonary hypertension of the newborn trial used a reduction in initiation of extracorporeal membrane oxygenation treatment as a primary end point, which is not feasible for other pediatric PAH trials. A Literature review revealed none of the existing noninvasive markers are fully validated as surrogates to assess PAH efficacy and long-term safety.

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CONFLICT OF INTEREST

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CONCLUSIONS—For pediatric PAH trials, clinical end points are acceptable, and novel validated surrogates would be helpful. FDA seeks collaboration with academia, industry and parents to develop other suitable and possibly more efficient efficacy end points to facilitate pediatric PAH drug development.

INTRODUCTION

Pulmonary hypertension is defined as the presence of abnormally high pulmonary artery pressures >25 mm Hg at rest or 30 mm Hg during exercise. It can occur in any age from newborns, infants to adults. When compared with adults, pediatric pulmonary arterial hypertension (PAH) presents different clinical manifestations and has a higher mortality. For example, pediatric PAH more frequently presents with severe disease including syncope, more accelerated disease progression, and a significantly shorter interval between symptom onset and time of diagnosis.[1] Pediatric PAH may be idiopathic, heritable or associated with congenital heart disease, but it is rarely caused by connective tissue disease. In contrast, adults with PAH are frequently associated with connective tissue disease.[2] As the natural history of PAH and response to treatment can differ in children and adults,[1] extrapolation of trial efficacy data from adults cannot be used. Data in children are needed to understand disease progression, survival and response to treatment.

Neonatal PAH differs from pediatric PAH in that it resolves in the majority of infants, and is usually not associated with genetic factors. A notable exception is alveolar capillary dysplasia with misalignment of lung vessels, a rare but lethal cause of pulmonary hypertension in the newborn.[3] Severe persistent pulmonary hypertension of the newborn (PPHN) has multiple causes but in general is a result of failing normal cardiopulmonary transition to achieve the normal neonatal systemic circulation. In general, PPHN can be characterized as one of three types that (1) the abnormally constricted pulmonary vasculature due to lung parenchymal disease such as meconium aspiration syndrome and respiratory distress syndrome; (2) the lung with normal parenchyma and remodeled pulmonary vasculature, also known as idiopathic PPHN; or (3) the hypoplastic vasculature as seen in congenital diaphragmatic hernia.[3] It is estimated that PPHN occurs in 0.2% of live born term infants.[3] PPHN complicates the course of ~ 10% of infants with respiratory failure, which is responsible for over one-third of all neonatal mortality.[3]

Currently, only INOmax has been approved for PPHN. In the United States, no drug has been approved for the treatment of pediatric PAH. The lack of developmentally appropriate efficacy end points and clinical trials contributes to this unmet medical need. To address this unmet medical demand, we reviewed the efficacy end points and surrogates[4] in the clinical trials that resulted in the Food and Drug Administration (FDA) approval of treatments for adult and pediatric PAH with the goal of determining if any of the adult end points are adaptable or applicable for children. In addition, we reviewed the biomarker literature to identify potential surrogate end points suitable for pediatric PAH trials.

MATERIALS AND METHODS

Review of trial data submitted to the FDA

The clinical trial data submitted from 1995 to 2013 were retrieved from FDA's Document Archiving, Reporting & Regulatory Tracking System or the document room (if the electronic copies were not available). The efficacy end points and surrogates of all clinical trials that led to FDA approval for indications in adult and/or pediatric PAH were reviewed. We evaluated these end points using children's developmental capability as a criterion to determine whether these study end points were suitable for pediatric PAH trials. We also reviewed the efficacy end points and surrogates of a pediatric PAH trial that resulted in non-approval. The data from each trial are presented in tables to compare the differences in study end points between pediatric and adult PAH trials.

Literature review of noninvasive biomarkers used in PAH

The electronic database, PubMed/Medline, was searched using the phrase '(pulmonary arterial hypertension) AND biomarkers/AND (treatment response)'. The last search was conducted on 7 August 2015. The noninvasive biomarkers were examined to explore potential surrogate end points based on the criteria described in the FDA Guidance for end point qualification process.[5] The purpose of the literature review was to understand the current state of the efficacy end points and surrogates used in the adult and pediatric PAH trials. The evidence found in the literature review was used as a reference to confirm or challenge what was found in the review of the clinical trials that led to FDA approval for indications in PAH.

RESULTS

Review of PAH registration trials submitted to the FDA

Nine drugs for PAH (bosentan, ambrisentan, sildenafil, tadalafil, treprostinil, iloprost, epoprostenol, macitentan and riociguat) are approved for adult PAH and 1 drug (INOmax) for PPHN. Although no drug was approved for pediatric PAH, sildenafil was studied in pediatric patients 1–17 years of age. As shown in Table 1, an increase in the 6 min walking distance (6MWD) was used as the primary end point in eight of nine adult PAH trials. Recently, a composite of time to the first morbidity or mortality event (TTFMME) was used as the primary end point in the macitentan trial for adult PAH, with a change in 6MWD relegated to secondary end point. The first morbidity or mortality events included (1) death, or (2) onset of a treatment-emergent adverse event with a fatal outcome occurring within 4 weeks of study treatment discontinuation, or (3) atrial septostomy or hospitalization for atrial septostomy, or (4) lung transplantation or hospitalization for lung transplantation, or (5) initiation of intravenous or subcutaneous prostanoids (for example, epoprostenol, treprostinil)/hospitalization for initiation of intravenous or subcutaneous prostanoids, or (6) other worsening of PAH. As shown in Table 1, reduction in initiation of extracorporeal membrane oxygenation (ECMO) treatment was used as primary end point in the INOmax approval for PPHN.

As shown in Table 1, sildenafil pediatric PAH trial used an increase in O_2 consumption at peak exercise at week 16 as the primary end point, but 51% of the enrolled children were unable to perform the necessary cardiopulmonary exercise testing. FDA internal analysis of 13 adult trials (n = 1096) and seven drugs in three different classes of PAH therapies has demonstrated that hemodynamic assessments of changes in pulmonary vascular resistance index (PVRi) and mean pulmonary artery pressure (mPAP) using right heart catheterization (RHC) correlate with Δ6MWD in adult PAH patients. This analysis also showed that treatment induced changes in PVRi was able to explain treatment induced Δ6MWD. Therefore, a change in PVRi or mPAP was used as a surrogate for the 6MWD to assess exercise capacity in pediatric PAH patients in the sildenafil trial as shown in Table 1. Two children died during pre-randomization owing to complications of the RHC hemodynamic measurements. Three additional children suffered severe adverse events as a consequence of the RHC hemodynamic assessments either during pre-randomization or at the end of study. In addition, long-term mortality showed a dose-related adverse trend on mortality. For these reasons, sildenafil was not approved for use in pediatric PAH.

Literature review of noninvasive biomarkers used in PAH

Of 326 retrieved biomarker publications relevant to PAH, we reviewed 88 that were relevant to right ventricular (RV) function assessment. The noninvasive measures include flow imaging modalities such as echocardiography, magnetic resonance imaging (MRI), and positron emission tomography (PET), along with electrical velocimetry and circulating biomarkers. These were studied to explore the possibility of serving as surrogate end points in PAH. Table 2 summarized the current investigation status of the properties (for example, ability to detect the change of treatment effect, correlation with clinical end points and validation and so on) of five promising noninvasive biomarkers based on the criteria for surrogate end points.[6] Particularly, in order to function as surrogates in the definitive efficacy trials, biomarkers need to be able to detect the change of treatment effect; be correlated with clinical end points; and validated in the definitive clinical trials.[6]

As ΔPVRi and ΔmPAP that are assessed by RHC can be used as surrogate end points to assess exercise capacity in the pediatric PAH trial and drug development, it would be helpful to determine whether echocardiography, MRI and PET imaging modalities could accurately measure PVR and mPAP and thus be used as an alternative to RHC for exercise capacity assessment. Echocardiography is the most important noninvasive tool that is used to detect and monitor PAH, though cardiac catheterization is commonly used to define PAH.[7,8] Echocardiography can reliably provide several estimates of hemodynamic function that closely correlate with those of RHC measurements.[9–11] Depended on assumptions of RV geometry, a variety of estimates of RV function can be made. For example, flattening and inversion of the inter-ventricular septum toward the left ventricle is highly suggestive of PAH.[9] Advancement in technology has provided new techniques for evaluating RV function (3D echocardiography, strain and strain rate) using echocardiography, but more data are needed in the pediatric population to determine the reproducibility of these new techniques.[8,9] In addition, tissue Doppler imaging has been used to predict adverse outcome in children with idiopathic PAH.[9,12] However, echocardiography is subject to significant

operator and interpretation variability,[13] thus presents a major limitation to be used as an alternative to RHC in the definitive PAH efficacy trials at the present time.

Cardiac MRI assesses RV morphology, and volumes and ejection fraction.[9,14,15] The ventricular mass index, which is the quotient of RV mass over left ventricular mass, is highly sensitive and specific for PAH prognosis.[9,16] When compared with echocardiography, MRI provides a higher spatial resolution and better inter-observer reproducibility and is currently considered as a preferred imaging modality for the detailed study of RV.[9,14] MRI has been used to assess right heart function and resistance of the pulmonary circulation in adults and pediatric patients with PAH.[17–19] The hemodynamic variables derived from MRI correlate with those assessed by RHC.[17–20] When compared with RHC, MRI provides a more complete picture of overall RV structure and function along with very useful information of pulmonary arterial pressure (PAP) and blood flow.[15] Some preliminary studies have shown that MRI is able to detect treatment responses with the potential to align functional and hemodynamic response measurements.[15,21–23] However MRI-based assessment needs further study and is currently not ready to replace RHC to define PAH diagnosis or to assess drug treatment effect.[15,24]

PET appears to be a suitable method for assessing RV function and myocardial glucose metabolism in adult patients with PAH.[9] Over the past decade, PET application has markedly increased in the setting of adult PAH. It was shown that pathologic myocardial glycolytic metabolism is quantitatively related to cardiac dysfunction in adult PAH over time.[25] In rat models, Glut1 upregulation in proliferation vascular cells in PAH results in increased lung fluorodeoxyglucose PET uptake.[26] Fluorodeoxyglucose PET is sensitive to mild PAH and can monitor therapeutic changes in the vasculature.[26] PET would be less suitable for infant and pediatric PAH patients owing to excessive radiation exposure.

Electrical velocimetry is a noninvasive method of continuous left cardiac output monitoring based on the measurement of thoracic electrical bio-impedance. It has been compared with invasive methods of cardiac output measurements, particularly thermo-dilution techniques, which have demonstrated 87% correlation in animal models, 85% in stable post-surgical adult patients and 80% in children with congenital heart defects.[27–29] Electrical velocimetry has also been compared with echocardiography in healthy term newborns during the first 2 postnatal days.[30] In this study, Noori *et al.*[30] has found that the precision of electrical velocimetry to be similar to the precision of echocardiography (31.6% vs 30%, respectively).

Many potential circulating markers that are related to heart failure, inflammation, homeostasis, remodeling and endothelial cell-smooth muscle cell interaction have been identified to assess disease severity and treatment response. Currently, all of these circulating biomarkers lack specificity, standardization and validation that are required as a surrogate end point. More studies are needed to demonstrate their potential use in children and infants with PAH. N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) is probably the most studied circulating protein biomarkers in PAH.[9] NT-pro-BNP has been shown to be a biomarker for disease severity in PAH. It has been studied to determine whether the baseline NT-pro-BNP levels correlated with improvement in 6MWD, in a randomized, placebo controlled, double-blind study of the inhaled treprostinil to oral therapy for 178

adults with PAH.[31] In this study, the authors found that baseline NT-pro-BNP levels had a strong interaction with treatment response in predicting change from baseline for 6MWD ($P<0.01$). Patients with high levels of NT-proBNP at baseline showed greater improvement in 6MWD after treprostinil treatment.[31] In addition, NT-pro-BNP has been used as an exploratory end point in the double-blind, randomized controlled PAH trials and was able to detect the treatment effects in these trials.[32,33]

In summary as shown in Table 2, although echocardiography, MRI, electrical velocimetry and the circulating level of NT-proBNP showed potential, none has been fully validated for the correlation with clinical end points and sensitivity of differential treatment effect to establish them as surrogate end points to assess efficacy and long-term safety.

DISCUSSION

Measurement of a treatment response is difficult to quantitate in pediatric PAH. There are challenges involved in performing and interpreting the traditional end points that are accepted for adults but not yet in children. However, composite of time to the first morbidity or mortality event could be considered as a potential end point in pediatric PAH trials. The availability of such clinical end points for pediatric PAH would be helpful but there is little evidence that these improvements correlate with a measure of performance. Gabler *et al.*[34] demonstrated that Δ6MWD failed to explain a large proportion of the treatment effect in clinical worsening event reduction, which indicated Δ6MWD an inadequate surrogate for the time to development of clinical worsening events. The 6MWD has value as a direct measure of adult exercise performance, and it has been used as primary efficacy end point in adult PAH trials. However, the 6MWD test is not reliable in children younger than 5 to 6 years and is less reproducible in children.[2] For these reasons, the 6MWD is not an appropriate measure of exercise performance in neonates, infants and young children. Reduction in initiation of ECMO is not appropriate for pediatric PAH trials. Although ECMO for neonates was managed under the same standard of inclusion/exclusion criteria and performance evaluation across all institutions, similar practice standards do not exist for ECMO in children. Cardiopulmonary exercise testing has failed as a primary end point in pediatric PAH trials because 51% of children were unable to perform it.

Although ΔPVRi and ΔmPAP were used as surrogate end points to assess exercise capacity in the pediatric PAH trial and drug development, these were not an adequate surrogate for the end point of the time to clinical worsening events.[35] Cardiac catheterization, a non-therapeutic procedure, remains the ‘gold standard’ for evaluating disease severity and treatment responses in children. Hemodynamic parameters have been shown to correlate with prognosis in children.[2] The safety of these procedures as surrogate end points for 6MWD is a major concern owing to the deaths and severe adverse events observed during hemodynamic assessments in the sildenafil pediatric trial. Thus, there are ethical concerns about using cardiac catheterization to obtain the PAP as the end point in future clinical trials. In summary, FDA does not recommend cardiac catheterization based hemodynamic parameters as an end point assessment in the pediatric trials at the present time.

Serial NT-proBNP and other plasma biomarker blood levels can be obtained relatively noninvasively and safely. Thus, noninvasive biomarkers are important for infant and pediatric PAH trials, but they must be validated and standardized to demonstrate specificity and reliability. Biomarkers in infant and pediatric 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, when compared with those of adults.[9] More studies are needed to fully validate the existing biomarkers as surrogates and perhaps to develop new promising clinical outcome assessment measures to assess treatment benefit, disease progression and long-term safety signals while reflecting the physiological development in children with PAH in the new era of the drug development.

From our review, no patient-reported outcome (PRO) has been used as a primary study end point for phase 3 trials to support approval of products intended to treat infant and pediatric PAH. PRO, one of the clinical outcome assessments, is a measurement based on a report that comes from the patient (that is, study subject) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (for example, pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others.[36] Owing to the complexity of the clinical manifestations in pediatric PAH and the impact of developmental and psychosocial issues on school-age children and adolescents, development of PRO instruments to measure how patients feel and function in pediatric PAH can be challenging although it might be helpful to measure signs and symptoms as well as health-related quality of life.

Actigraphy is a mobile device that can directly, noninvasively and readily measure continuous physical activity in the real life outpatient setting.[37–39] A recent pilot study in adults with severe PAH suggests that actigraphy data are associated with survival, and may be helpful for longitudinal assessments of changes in disease status.[39] The actigraphy activity counts were also correlated with 6MWD test in adults with PAH (Spearman rank correlation = 0.72, $P<0.001$).[40] However, studies need to be conducted in pediatric PAH patients in order to explore the possibility of using actigraphy as an efficacy end point in pediatric PAH trials and drug development. Actigraphy would be a feasible and noninvasive study end point for infant and pediatric PAH clinical trials and drug development if proven to be reliable and strongly predictive of the clinical course and outcomes in infant and pediatric PAH.

The limitation in pediatric patient enrollment is another major challenge for conducting PAH trials in children and neonates. Globalization of the effort and the participation of the American Academy of Pediatrics Section on Neonatal-Perinatal Medicine, pediatric cardiologists, clinical neonatologists, parents/community and National Institutes of Health would be very helpful to combine resources for future PAH trials in children and neonates.

In conclusion, clinical end points are clearly acceptable for pediatric PAH trials. The FDA supports collaboration among academia, industry and government to develop/identify,

validate and qualify suitable and possibly more efficient efficacy end points to facilitate drug development for children and neonates with PAH. The FDA also seeks input and collaboration with families who understand the critical need for effective therapies to improve outcomes for children and neonates.

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Table 1

Summary of efficacy end points used in the PAH trials submitted to the FDA

End points used	Types of end points	Study population and numbers of products approved (*n*)	Products approved	Suitability for pediatric trials	Major limitations
Increase in 6 min walking distance	Primary end point	Adults (*n* = 8)	Bosentan; ambrisentan; sildenafil; tadalafil; treprostinil, iloprost, epoprostenol; riociguat	Partial	Not reliable in children ≤ 5 years No normal ref <4 years Not applicable in infants
A composite of time to the 1st morbidity or mortality event	Primary end point	Adults (*n* = 1)	Macitentan	Yes	Need to optimize and define relevant components of clinical worsening in pediatric PAH patients
Reduction in initiation of ECMO treatment	Primary end point	Neonates (*n* = 1)	INOmax	No	No similar standard of the care in children
Increase in O_2 consumption at peak exercise via CPET	Primary end point	Pediatrics (*n* = 1)	Sildenafil *	Partial	51% of children were developmentally unable to perform CPET in this trial
ΔPVRi or ΔmPAP assessed by RHC	Surrogates	Pediatrics (*n* = 1)	Sildenafil *	Yes	Two death and three severe adverse events were observed during RHC

Abbreviations: CPET, cardiopulmonary exercise testing; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; ΔPVRi, change in pulmonary vascular resistance index; ΔmPAP, change in mean pulmonary arterial pressure.

* Not approved for use in pediatric PAH.

Table 2

Evaluation of five promising noninvasive biomarkers as potential surrogate end points for pediatric PAH trials

Noninvasive biomarkers	Measurement function	Drug effect detection	Correlation with 6MWD or RHC mPAP/PVRi	Validation in definitive RCT	Major potential limitations
Echocardiography	Diagnosis tool for heart function and shape; cardiopulmonary hemodynamics	Not studied	Tricuspid Em and mPAP correlation: $r = -0.67$, $P<0.001$; RV peak strain and PVR correlation: $r = 0.73$, $P<0.001$	Not studied	Subject to significant operator variability; variable intra and inter-reader reliability
MRI	Cardiopulmonary Hemodynamic Measure	Yes	Correlation between RHC and MRI derived mPAP: $r = 0.92$ Average blood velocity had the best correlation with RHC mPAP and PVRi: $r = -0.86$, $P<0.001$	Not adequate	Sedation in young children; Long scan time and incompatibility with metal compounds such as the delivery pump
PET	RV function and myocardial glucose metabolism	Not studied	Not well established	Not studied	Less suitable for pediatric patients due to radio-active isotope exposure
Electrical Velocimetry	Cardiac Output Measure	Not studied	Comparable with left ventricular output measured by echocardiography	Not studied	Not studied in PAH condition
NT-proBNP	RV failure	Yes	mPAP ($r = 0.47$, $P<0.001$); PVR ($r = 0.66$, $P<0.001$); 6MWD ($r = 0.6$, $P<0.001$)	Not adequate	Impacted by demographic characteristics, renal insufficiency and etiology of PAH.

Abbreviations: 6MWD, 6 min walking distance; mPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricular; Tricuspid Em, Tricuspid early diastolic myocardial relaxation velocity.