Challenges in Endpoint Development for Pulmonary Hypertension Trials in Children

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There are currently 12 medications approved for use in the treatment of pulmonary arterial hypertension (PAH) in adults. These include endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, and prostacyclins. However, in children there are no approved targeted PAH medications, with the exception of inhaled nitric oxide for treatment of hypoxemic respiratory failure in neonates. This review will address some of the challenges in the development of treatments for children, including lessons from recent trials, endpoints for clinical trials, and challenges with drug approval in children.

Impediments to enrolling children in clinical trials are many. Pulmonary hypertension (PH) is a rare disorder in adults and even less common in children.[1] For example, idiopathic pulmonary arterial hypertension (IPAH) is a rare disease with an incidence of 1 to 2 per million adults. The incidence of IPAH in children is 0.7 cases per million children.[2] Physicians often prescribe drugs approved for use in adults off label in children. Furthermore, parents are reluctant to enroll children with a serious disabling and progressive disease in a controlled clinical trial, especially one in which the child may receive a placebo. Children are considered a vulnerable population; they are developmentally, physiologically, and psychologically different than adults, thereby complicating research efforts.[3] Investigators and federal agencies are very reluctant to perform a study in children that may be associated with increased risk. An example is the recent US Food and Drug Administration (FDA) decision to exclude cardiac catheterization from PH clinical trials in children. The FDA made this decision because there was a greater risk of death in children with PH. Although the risk is difficult to quantify, it appears to equal about 1%.[4] There are also consent issues, as parents should provide consent and children over 7 years of age must assent. These issues lead to slow enrollment.

The primary endpoint of most adult pulmonary arterial hypertension (PAH) trials has almost exclusively been exercise capacity as assessed by the 6-minute walk test,[5-12] a combined measure including the 6-minute walk,[13] and (more recently) event-driven trials.[14] A single trial used cardiopulmonary exercise testing[15]; however, this endpoint was abandoned since the trial was negative. Secondary endpoints frequently include hemodynamics, functional class, quality of life, and biomarkers such as brain natriuretic peptide (BNP).

One of the first studies in children was the BREATHE-3 (Bosentan Randomized trial of Endothelin Antagonist THErapy for pulmonary hypertension) trial of bosentan.[16] This was an open-label 12-week study of 19 children; dosing was empiric and based on adult levels. Study endpoints included pharmacokinetics, safety, and cardiac catheterization parameters. The study revealed valuable information on dosing and safety. Catheterization parameters were significant; however, these data were not sufficient for labeling. Subsequent studies of bosentan focused on pharmacokinetics of a novel formulation of bosentan in children with PAH. In the FUTURE-1 (Pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion) study, the pharmacokinetics of bosentan at doses of 2 mg/kg twice a day was compared with 4 mg/kg twice a day, and revealed no difference in drug exposure.[17] The FUTURE-3 study evaluated pharmacokinetics, tolerability, safety, and efficacy of the pediatric formulation of bosentan twice vs 3 times a day.

The STARTS-1 (Sildenafil in Treatment-naïve Children, aged 1-17 years, with Pulmonary Arterial Hypertension) pediatric trial was a landmark study, as it was the first randomized, double-blind, placebo-controlled, and dose-ranging parallel group study of a PH drug in children.[18] It also highlights many of the problems inherent in a pediatric PH trial. The patient population was treatment-naïve children aged 1 to 17 years with PAH. The trial began enrollment in August 2003, and completed in February 2008. Thus, it took more than 5 years to enroll a sufficient number of patients to be tested for the primary endpoint: to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in pediatric patients with PAH, as measured by exercise tolerance using bicycle ergometry testing only in those subjects able to perform the exercise test. Just about half of the children enrolled could perform the bicycle ergometry test. All children had cardiac catheterization. The primary efficacy endpoint was the percent change from baseline in peak oxygen consumption at Week 16, with main secondary endpoints of change from baseline in mean pulmonary artery pressure and pulmonary vascular resistance index. Patients were randomized to placebo, low-dose, medium-dose, or high-dose sildenafil and treated for a

total of 16 weeks. Cardiac catheterization and exercise testing were performed after 16 weeks of therapy. The trial did not meet its primary endpoint, which was the combined change in placebo-adjusted percent change in peak oxygen consumption (P=0.056). There were improvements in some parameters of pulmonary pressure and pulmonary vascular resistance. After the 16 weeks, patients in the low-, medium-, and high-dose groups remained on that dose. Patients in the placebo group were randomized to low, medium, or high dose; patients were then followed for the duration of the study. If the patient required additional therapy, he/she was discontinued. The controversy with the study arose when mortality was evaluated on a yearly basis. At 1 year, only 1 patient had died in the high-dose group. By 2 years, there was a trend for an increase in mortality in the high-dose group. By 3 years, the hazard ratio for mortality was 3.95 (95% confidence interval, 1.46-10.65) for high vs low dose. Most patients who died (28/37) had idiopathic/heritable PAH (76% vs 33% overall) and baseline functional class III/IV disease (38% vs 15% overall); patients who died had worse baseline hemodynamics. Kaplan-Meier estimated 3-year survival rates from the start of sildenafil were 94%, 93%, and 88% for patients randomized to low-, medium-, and high-dose sildenafil.[19] Based on this, the data monitoring committee recommended that all patients down-titrate from the high dose.

Review of the STARTS-1 and -2 data by the FDA and the European Medicines Agency (EMA) resulted in disparate recommendations. Sildenafil was approved by the EMA in 2011, with a later warning on avoidance of use of the high dose. In August 2012, the FDA released a strong warning against the (chronic) use of sildenafil for pediatric patients (ages 1 through 17) with PAH (http://www.fda.gov/Safety/Med Watch/SafetyInformation/SafetyAlerts forHumanMedicalProducts/ucm317743. htm). The warning stated that "... *this recommendation against (sildenafil) use is based on a recent long-term clinical pediatric trial showing that: (1) children taking a high dose of Revatio had a higher risk of death than children taking a low dose, and (2) the low doses of Revatio are not effective in improving exercise ability. Revatio has never been approved for the treatment of PAH in children, and in light of the new clinical trial information, off-label (not approved by FDA) use of the drug in pediatric patients is not recommended . . . ."* The results of the STARTS-2 trial are difficult to interpret: 1) there was no placebo group included; 2) doses of sildenafil changed during the study; 3) patients requiring additional PAH therapy were withdrawn; 4) children were not censored once withdrawn from the study to add therapy or because of withdrawal of consent, but continued to be followed; 5) the mortality signal was not consistent across weight groups or etiologies. Children 8-20 kg did not have an increase in mortality with high-dose sildenafil, nor did patients with congenital heart disease. The study ended in December 2012; at that time, there were 42 deaths: 18% of the total. In the low-dose groups, mortality was 9.1%; in the medium-dose group, mortality was 17.6%; and in the high-dose group, mortality was 24%. Following a meeting with the FDA by members of the American Heart Association, American College of Cardiology, and American Academy of Pediatrics, the FDA clarified the sildenafil warning, stating that there may be situations in which the risk-benefit profile of Revatio may be acceptable in individual children, and that sildenafil is still not recommended in children with PH. The statement further indicates that the initial recommendation was not intended to suggest that Revatio should *never* be used in children (http://www.fda.gov/Drugs/ DrugSafety/ucm390876.htm).

Other biomarkers have been evaluated in children with PAH and may be used as secondary endpoints. Several studies have evaluated the levels of BNP/N-terminal pro-BNP (NT-proBNP) in children with PAH, and found that those children with a higher value have an increase in mortality.[20-22] In the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), older age at diagnosis, cardiac index at diagnosis, and pulmonary vascular resistance index at diagnosis were associated with worse survival.[23] In the Netherlands registry, mortality variables associated with increased mortality included increased World Health Organization (WHO) functional class (WHO-FC), decreased systolic blood pressure, increased pulmonary to systemic arterial pressure ratio, increased NT-proBNP, and increased uric acid.[24] Worse survival has consistently been associated with worse WHO-FC in children.[23-26] Furthermore, hemodynamic parameters are associated with survival.[26,27] Imaging studies such as cardiac MRI and tissue Doppler evaluation are also predictive of outcome.[28,29] Other clinically relevant endpoints might include growth parameters and quality-of-life questionnaires.[30] A fault of these studies is that treatment-induced changes were not shown. Recently a study in the Netherlands has shown that the variables of WHO-FC, NT-proBNP, and tricuspid annular plane systolic excursion by echocardiography were identified as follow-up predictors in which treatment-induced changes were associated with survival.[30]

Exercise capacity is of particular interest, as it satisfies the FDA requirements that drugs make patients feel better and live longer. The challenge with 6-minute walk distance is that children are not reliable in performing this test and sometimes run for parts of the test. Baseline 6-minute walk distance is not a predictor of survival, neither when expressed as an absolute distance in meters nor when adjusted to reference values expressed as z-score or as percentage of predicted value.[22,24,25,31,32] Cardiopulmonary exercise testing still has a potential role, but has not been proven to be a surrogate; the only pediatric trial in which it was used, the STARTS-1 trial, did not meet the primary endpoint.

Future clinical trials should be designed to be informative for practicing physicians. They should include safety, pharmacokinetics, a measure of efficacy, and cardiac catheterization in a subpopulation. An efficacy endpoint is needed, particularly if there is a desire to obtain labeling, and for industry to obtain a patent extension. The EMA has mandated a pediatric investigational plan

(PIP) for all new drugs. A PIP is a development plan intended to ensure that the necessary data are obtained through studies to support the authorization of a medicine for children. In the US, pediatric PAH is an orphan disease, and therefore there is no mandate for study. The requirements for a patent extension are rigorous and require a robust efficacy trial. Time to clinical worsening or event-driven trials have shown promise in adult PH. The macitentan-SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome) trial utilized a morbidity and mortality primary endpoint that included the time from the initiation of treatment to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH.[14] A similar design is appealing in pediatrics because it allows for a clinical worsening event-driven trial that would not require a single primary validated endpoint. Disadvantages of this trial design would include the need for a large number of patients to meet an endpoint. These trials would take several years and would likely require multiple doses to satisfy the concern of a dose-response increase in mortality with sildenafil.

In conclusion, PAH trials are difficult to perform in children for many reasons. Both consent and assent are required; inclusion of a placebo arm is challenging for parents to accept; and an efficacy trial is difficult to perform due to the small number of patients involved. A hemodynamic or exercise primary endpoint is problematic since not all patients are evaluable, and the FDA has limited the use of catheterization in approved clinical trials. Safety and pharmacokinetic parameters are important evaluations in any pediatric trial. An event-driven trial is more appealing, but will take years to enroll and complete.

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