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Review

Challenges of designing multicenter trials in pediatric heart failure

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ABSTRACT

Designing clinical trials in pediatric heart failure presents challenges in many aspects of study design and implementation. These stem from the fact that the underlying mechanisms and clinical manifestations of heart failure in children are heterogenous, clinical outcome measures have not been well characterized, and the power to detect clinically important endpoints is limited by the small number of affected patients. The mechanisms of heart failure in children are often radically different than those seen in adults and justifying the study rationale for the use of an adult heart failure medication to children can be challenging. The identification of valid clinical endpoints is limited by a lack of natural history data and the length of time required to reach a clinical outcome can be difficult to incorporate into a clinical trial timeframe. Trial enrollment can be hindered by a lack of equipoise and parental reluctance to agree to study tests. The Federal Drug Administration and European Medicines Authority (EMA) have instituted several measures to encourage the study of new drugs in children with heart failure. These include extending market exclusivity following performance of an approved study in children with heart failure and, in the case of the EMA, requiring approval of a pediatric investigational protocol prior to granting approval for the use of a new medication in the adult population. The challenges of designing clinical trials in pediatric heart failure can only be overcome by a collaborative approach amongst investigators, patients, governmental agencies and pharmaceutical companies.

1. Clinical Trials in Pediatric Heart Failure

There is a pressing need for safety and efficacy data to support the use of drugs to treat pediatric heart failure. Data indicate that 23–60% of medications in use in children have not been studied for safety or efficacy [1]. In the United States and Europe, the impetus to perform drug trials in children has received significant regulatory support through the Federal Drug Administration (FDA) Best Pharmaceuticals for Children (BPCA) and the Pediatric Research Equity Act (PRA) and the European Medicines Authority (EMA) Paediatric Regulation No. 1901/2006 of the European Parliament and of the Council on Medicinal Products for pediatric use [2–4]. Both the FDA and EMA use a "carrot and stick" approach. The BPCA rewards the manufacturer with an extension of patent exclusivity following completion of an approved protocol. The PREA requires a manufacturer to submit a pediatric assessment for any formulation with a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration or be subject to fines. The EMA has gone one step further and requires approval of a pediatric investigational plan prior to the approval of a new drug for use in the adult population. The EMA also offers 6-month extension to the Supplementary Protection Certificate for successful completion of the pediatric study or an additional 2 years of market exclusivity for orphan drugs. Both the FDA and EMA have provisions for waiving the pediatric regulations if it is determined that pediatric use would be unsafe or ineffective. The FDA and European Union have also used funding mechanisms to stimulate development and authorization of off-patent medicines [5,6].

These regulations have had an impact on the performance of clinical drug trials in children with 1000 medications receiving FDA approval for use in children between 2003–2009 and 394 label changes to include pediatric indications between 1998–2010 [7]. Of the cardiovascular drugs studied as part of the BPCA act, only 45% of the studies were positive and no effect of the drug was found in 55% [8]. Pediatric exclusivity had been granted for 178 drugs through 2010 with a median benefit to the manufacturer of $134 million [9]. In order to encourage research in off-label drugs, the NIH and FDA have also developed a priority list updated yearly until 2009 [10]. The EMA has developed funding mechanisms to encourage multicenter research in drug discovery and development in children [5].

2. Challenges in Study Design

Designing clinical trials in pediatric heart failure is challenging from virtually all aspects of study design and implementation. The underlying mechanisms and clinical manifestations of heart failure in children are heterogenous and in many instances have not been well characterized [11,12]. The population is rare, limiting the power to detect clinically

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important endpoints within a reasonable time frame [13–16]. In addition, the incidence of clinically relevant endpoints is lower than seen in adults and surrogate endpoints have not been well validated. Therapies with demonstrable benefit in the adult population often require modifications to accommodate child-friendly methods of drug delivery or the smaller body sizes found in the growing child [6]. Concerns regarding patient safety in the vulnerable pediatric population can be an obstacle to the study of novel therapies in the absence of data from the adult population. Research infrastructure is not as robust in support of pediatric trials, as start-up costs are often substantial relative to the expected patient enrollment at an individual center [6].

2.1. Study Rationale

The rationale to study an intervention in children is commonly based on data demonstrating benefit in the adult population [17]. This can present challenges in the pediatric heart failure population, as adults participating in randomized clinical heart failure trials are older, predominantly male, with a substantial proportion having underlying ischemic heart disease [18,19]. They have a high incidence of co-morbidities such as hypertension or renal dysfunction that may alter the therapeutic response or the incidence of adverse events [19,20]. Clinical outcome events such as death or worsening heart failure are common in the adult heart failure population, with incidences of 25–30% in enrolled patients within a year in many studies [18,21].

The mechanisms of pediatric heart failure are heterogenous and range from primary myocardial systolic dysfunction in dilated cardiomyopathy to structural abnormalities in patients with single ventricle [11]. Increasingly, genetic abnormalities are being identified in pediatric cardiomyopathy patients that result in systolic and/or diastolic dysfunction [22]. In complex congenital heart disease, ventricular morphology is often abnormal in addition to systolic dysfunction and arrhythmias and cyanosis can contribute to the development or severity of heart failure [16,23,24]. There is some evidence to support disruption of the neurohumoral axis in pediatric heart failure due to systolic ventricular dysfunction, however in patients with structural heart disease the data is conflicting [25–28]. The overall incidence of hard clinical endpoints such as death or transplantation is lower than that found in the adult population, and these endpoints can be rare in mildly symptomatic children [29–33].

Support for hypotheses generated by extrapolation of therapeutic benefit from adult studies to children may be weak because of these underlying differences in the patient populations [24]. The justification for a particular intervention can be difficult because of limitations in study feasibility due to a lower incidence of predicted clinical events in the nonintervention group and a high risk to benefit ratio.

2.2. Study Population: Acute or Chronic Heart Failure

Heart failure therapies can be distinguished by whether the intended benefit is in the acute decompensated heart failure or chronic heart failure population. Acute decompensated heart failure occurs most commonly in two different settings in the pediatric population. Children with dilated cardiomyopathy can present or develop an exacerbation of acute decompensated heart failure. Neonates and infants with congenital heart disease also manifest the signs and symptoms of acute decompensated heart failure in the early postoperative period following open heart surgery [34,35]. Both these populations offer the opportunity for the study of acute heart failure drugs, however it is challenging to combine the two populations for study because of the differences in clinical endpoints. Patients with dilated cardiomyopathy and acute decompensated heart failure have an 18–25% chance of progressing to death or transplantation within the year [13,33]. Infants and neonates with acute decompensated heart failure following open heart surgery often improve over time as the myocardium recovers. In the patient with single ventricle physiology the signs and symptoms of fluid overload may be a result of the high systemic venous pressures inherent in the underlying pathophysiology of the Fontan procedure and not related to myocardial dysfunction [14,36].

Chronic heart failure is common in the child with a dilated cardiomyopathy and less common in the patient with congenital heart disease. Chronic heart failure in the child with congenital heart disease is most common in patients with single ventricle physiology [37]. The incidence of clinical endpoints in the mildly symptomatic, stable heart failure population is low, presenting challenges for study feasibility when assessing a chronic heart failure medication [29,38]. In some cases, the signs and symptoms of chronic heart failure that are seen in the single ventricle population can be attributed to the underlying Fontan physiology and may occur in patients with normal ventricular function.

Intervention trials require well-defined inclusion and exclusion criteria to identify the eligible study population. In children with heart failure, the incidence of clinical signs and symptoms, echocardiographic measures and other biomarkers of heart failure seen in the specific target population is often not available. The incidence of common exclusion criteria such as renal or hepatic dysfunction, other co-morbidities and prior therapies is often not available. Without this data, accurate estimates of potential eligible subjects are challenging and can limit the validity of study feasibility predictions.

2.3. Outcome Measures

The identification and justification of clinically relevant outcome measures to assess benefit in clinical trials in pediatric heart failure is one of the most difficult tasks in clinical trial design in this population. Data regarding clinically important and easily measurable outcomes such as death, heart transplantation or mechanical assist device support are often available for the general population of children with heart failure [13,14,26,33,39–42]. Similar to the challenges faced when identifying inclusion and exclusion criteria, the incidence of clinical outcomes for the population meeting the inclusion and exclusion criteria for a particular study is rarely available. Data can be extrapolated from available studies, however analyses of registry data commonly span the full clinical spectrum of a disease and retrospective studies often include historical data that may not reflect current practice. Substantial practice variation is often present within registries and among single center studies that limit the generalizability of the outcomes reported.

The incidence of a single clinical outcome in the pediatric heart failure population is often too low to ensure completion of the study in a reasonable time frame due to the high number of patients required to demonstrate a treatment effect. Composite outcomes that include an assessment of clinical status in addition to the clinical outcomes have been used to increase endpoint determination [29]. The use of heart failure class or parental/physician assessments of clinical status introduces a measure of subjectivity that is difficult to standardize and can impact on the power of the study to detect a treatment effect [43]. Quantifiable markers of clinical course, or laboratory markers such as echocardiographic or MRI ventricular measurements or neurohumoral biomarkers have been proposed as surrogates for clinical outcomes (Table 1). None of these have been prospectively validated against clinical outcomes. A major limitation for the use of a surrogate marker is lack of data regarding the expected change over time. Data from adult heart failure studies may not be available or unable to be extrapolated to the pediatric study population. If expected changes in the nonintervention group cannot be accurately predicted, estimation of a potential treatment effect is challenging and may lead to underestimation of the power of the study and negatively impact study feasibility.

2.4. Enrollment

Enrolling pediatric heart failure patients in an intervention study can be challenging [44]. Screening and obtaining informed consent in