Promoting Clinical Trials on Pediatric Chronic Kidney Disease

By Howard Trachtman

The need

Chronic kidney disease (CKD) is a rare but serious condition in children and adolescents (1). The causes of CKD often differ from those that are common in adults with a far greater contribution of congenital abnormalities of the kidney and urinary tract (CAKUT) and a far less significance for diabetes and hypertensive nephrosclerosis. Although CKD is not nearly as prevalent in children as in adults, the effects on well-being and long-term health outcomes are just as profound in the pediatric population (2).

First, a recent study indicates that the natural history of glomerular disorders like focal segmental glomerulosclerosis (FSGS) is very similar in children, adolescents, and adults with a parallel trajectory of estimated glomerular filtration rate decline over time in the three age groups (3). Second, the onset of CKD early in life can have a wide range of irreversible, deleterious effects on somatic and neurocognitive development (4, 5). CKD in childhood interferes with normal pubertal development and the attainment of full growth stature. Finally, adolescence can be associated with compromised adherence to prescribed treatments leading to suboptimal care (6). Except for a few genetic disorders, such as oxalosis and atypical hemolytic uremic syndrome, there are no U.S. Food & Drug Administration (FDA)-approved therapies for pediatric CKD. This results in off-label use of most medications without clear-cut guidelines about indication and dosage. Taken together, all of these considerations argue persuasively for the need to conduct well-designed clinical trials in the pediatric population for those with CKD.

Because this is a rare condition, it will require innovative design and analytic approaches to enhance the feasibility and successful completion of proposed trials. Closer engagement with the patient community will be needed to foster their full participation in this effort.

Bioethical considerations

It is essential that clinical trials for pediatric CKD be conducted within a sound bioethical framework. There is a justifiable concern when testing novel therapies in neonates, children, and adolescents who represent a vulnerable population, but one that is in need of more effective therapeutics. The risks of adverse effects that may have long-term ramifications are greater in children than in adults. The concerns about disrupting normal development are unique to childhood. The uncertainty about whether children, adolescents, and their families fully comprehend the nature of their disease and about the potential hazards and benefits of a clinical trial needs to be taken into account in planning trials for pediatric CKD. However, this caution needs to be balanced by consideration of the actual impact of the disease in children versus adults. Additional studies like the one by Gipson et al. (3) would fill gaps in knowledge and provide a strong rationale for inclusion of pediatric patients in clinical trials. Performing additional studies would be relevant in a number of diseases such as autosomal-dominant polycystic kidney disease, Alport syndrome, and diabetic kidney disease, which begin at birth or in childhood. Finally, more attention to the lived experience of pediatric patients with CKD and a broader assessment of perceived risk and benefit by patients and care providers would promote a more grounded analysis of the ethical justification for testing novel therapies in pediatric patients. Autonomy is a dynamic variable in pediatrics, and the voices and wishes of adolescents regarding their participation in trials need to be heard.

Approaches

• **Patient identification:** The are a number of approaches that can be adopted to foster the conduct of clinical trials in pediatric CKD. Early case identification is critical to enable the documentation of patients who might qualify for enrollment in trials. Because of the relative rarity of CKD in children, routine measurement of serum creatinine concentration and urinary protein excretion is less likely to be routinely performed in children than in adults. However, computable phenotypes have been developed for identification of cases of glomerular disease and nephrotic syndrome using the electronic health record (7). Expanding these methods to include CKD would broaden the population to include glomerular and non-glomerular diseases, an important consideration in pediatrics.

In addition, it is important to educate and engage prospective trial participants about the clinical significance of CKD. This condition is often clinically silent without evident symptoms and, thus, unrecognized in its initial stages, and the adverse consequences are not fully appreciated. Moreover, children and adults are different, and the community should be made to understand the need to define optimal therapies specifically in children and adolescents. There is a great need to target these efforts to 1) minority and underrepresented populations who are wary of participating in trials due to historical and present-day injustices in the health care system and 2) misinformed populations who are wary of participating in clinical trials due to medical misinformation and inaccurate open-source content.

• **Registries:** Regional, national, and international registries represent an invaluable resource to assess the incidence, prevalence, and geographical distribution of kidney diseases in children (8). Importantly, these joint enterprises help delineate the natural history of the specific entities, a key consideration in clinical trial design and the estimation of the projected benefit of a new test therapy. Prominent examples include the European registry for autosomal recessive polycystic kidney disease and the PodoNet (Clinical, Genetic and Experimental Research into Hereditary Diseases of the Podocyte) registry for steroid-resistant nephrotic syndrome. Longitudinal, observational, cohort studies NEPTUNE (9) and CureGN (10) amplify this effort by compiling deep clinical and laboratory phenotyping of enrolled patients—in this case, children with nephrotic syndrome. Similar efforts need to be extended to the sizable number of children with CAKUT, which like FSGS, probably represents a heterogeneous group of disorders with distinctive mechanisms of kidney injury and damage. This will advance the scientific understanding of this disorder and lay the groundwork for more effective therapies.

Trial design

Because of the rarity of CKD in children, it is imperative that the trial design is optimized to help ensure successful enrollment and completion of studies. Novel approaches to dose finding and planned transition from phase 2 to phase 3 trials can expedite the successful completion of trials and minimize the sample size required. The definition of appropriate end points to assess efficacy of novel therapies is a vital concern in pediatric CKD because the rate of disease progression and the incidence of clinically relevant events are less than in adults. Examples include validated measures of oxalate excretion in clinical trials for primary hyperoxaluria (11). Incorporation of novel measures such as patient-reported outcomes may be especially pertinent in pediatric CKD. Adaptive designs and Sequential, Multiple Assignment, Randomized Trials (SMART) approaches are relevant in pediatric CKD because the limited number of patients reinforces the need to maximize what can be learned from each trial participant (12). Platform trials with an adaptive design, a common protocol, harmonized methods for sample acquisition and outcomes, and a concurrent control group would improve the efficiency of clinical trials in pediatric CKD (13). The designation of select pediatric nephrology divisions as clinical trial centers of excellence may provide a way to direct financial and institutional resources to those sites that are most likely to succeed in this work.

Extrapolation and in vitro studies

Because of the limited number of pediatric patients with CKD and the extent of resources available to conduct clinical trials, alternative sources of information can be used to guide the implementation of clinical trials. Extrapolation from adult clinical trials and trial experience may be warranted in circumstances where the mechanism of action and handling of the drug are likely to be similar in children and adults. In addition, newer technologies such as organoids or Kidney on a Chip provide in vitro models to test the efficacy of new agents in modest numbers of patients that can shed light on potential application in pediatric CKD. The FDA has provided guidance for clinical investigators to ensure that they use these non-standard methods in an appropriate and meaningful manner (14).

Initiatives

A number of initiatives are underway to meet the urgent challenge of promoting clinical trials in pediatric CKD. The Kidney Health Initiative (KHI) is a program sponsored by ASN that brings together nephrologists, industry partners, and the FDA into a shared space where they can discuss and implement strategies to facilitate clinical trials in nephrology. A Pediatric Working Group within the KHI is charged with addressing these issues from a pediatric perspective. Work is underway to survey key stakeholders about areas of priority for research in three distinct areas: 1) CKD in general, 2) transplantation, and 3) rare diseases. As a timely example, the importance of evaluating sodium-glucose cotransporter-2 inhibitors (SGLT2is) for the treatment of pediatric CKD has emerged as a significant clinical problem that warrants immediate attention. Although SGLT2is have been demonstrated to be safe and effective renoprotective agents in nearly all forms of adult CKD, there are limited data in children, underscoring the need to address this issue in a timely manner with well-designed, feasible trials.

In addition, the KHI Pediatric Working Group is

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Fosl1 Is Upregulated During AKI and Ameliorates Proximal Tubule Injury via α-Klotho

By Ignacio Portales-Castillo and Javier A. Neyra

Acute kidney injury (AKI) is a common condition that is characterized by necrosis of certain renal tubular cells, particularly in the proximal tubule, as well as modification of cellular signaling in remaining tubular cells to promote tissue repair. Nonetheless, the clinical context, severity, and duration of AKI may contribute to irreversible kidney parenchymal damage and fibrosis, which ultimately leads to chronic kidney disease. At the cellular level, evidence of failed proximal tubule repair includes persistent expression of markers such as the hepatitis A virus cellular receptor (Fvz1), keratin 20 (Krt20), and the vascular cell adhesion molecule 1 (VCAM1) [1]. Therefore, an area of considerable interest is the identification of protective cellular signatures during AKI.

In a recent issue of Kidney International, Cuarental et al. (2) used proximal tubule cell models as well as rodent models of AKI to identify a significant and consistent upregulation of Fosl1 during the early phase of kidney injury. Fosl1 is a leucine zipper protein that forms part of the canonical activator protein-1 transcription factor complex. The authors demonstrated that Fosl1 is abundant in the proximal tubule cells and can bind directly to the α-klotho gene to promote its expression. To study the relevance of Fosl1 during AKI, the authors selectively deleted Fosl1 in the proximal tubule. Compared with wild-type (WT) mice, Fosl1-deficient mice had more severe kidney injury after exposure to either cisplatin or folic acid, which is consistent with a protective role of Fosl1 during AKI. As would be predicted, mice lacking Fosl1

References