Systematically Evaluating SGLT2 Inhibitors in Children: An Interview with Howard Trachtman

By Karen Blum

In July, NephCure and the Kidney Health Initiative (KHI) convened a workshop of more than 75 nephrologists and Food and Drug Administration (FDA) and industry representatives from the United States and Europe to discuss the best potential use of sodium-glucose cotransporter-2 (SGLT2) inhibitors in pediatric patients with chronic kidney disease (CKD). *Kidney News* spoke with pediatric nephrologist and workshop Steering Committee member Howard Trachtman, MD, FASN, adjunct professor of pediatrics at the University of Michigan, to learn more about the outcomes of the workshop and next steps. Dr. Trachtman thanks co-members of the workshop Steering Committee William E. Smoyer, MD, FASN, and Debbie Gipson, MD, MS. (Responses have been lightly edited for brevity.)

Kidney News: **What was the impetus for holding this workshop?**

Trachtman: SGLT2 inhibitors have proven to be landmark drugs that have a clear-cut, beneficial effect on cardiovascular and renal outcomes in patients with kidney diseases due to type 2 diabetes. Now, clinical trials such as DAPA-CKD and EMPA-KIDNEY are demonstrating that this class of drugs is beneficial for nearly all causes of underlying CKD. As a result, SGLT2 inhibitors are being used as the standard of care for patients with CKD. However, there has been no organized, systematic effort to evaluate these drugs in the pediatric population. The workshop was convened with all of the relevant stakeholders to ask questions such as: Is there a need for clinical trials of SGLT2 inhibitors in pediatric CKD? Can we extrapolate data from adults to pediatric patients with CKD? If not, what specific populations, endpoints, and safety concerns should guide future trials to ensure that the drugs are used in a thoughtful way in pediatric patients with CKD?

If successful in our goals, we will [...] execute meaningful clinical trials that clarify the best way to treat the full range of pediatric patients with CKD.

Kidney News: **How commonly are the drugs being used off-label in pediatric populations?**

Trachtman: We were apprised of data from PEDSnet, a database from a consortium of eight nationally recognized pediatric centers across the United States that monitors over 8 million children. When reviewing off-label use of SGLT2 inhibitors in 2022, 10% occurred in patients treated by nephrologists and was more common in endocrinology and cardiology clinics. We think that off-label prescription is not the optimal way to treat children because it is not guided by high-quality evidence. It is best to know the efficacy and to define the optimal dose of SGLT2 inhibitors so that children and adolescents are given therapy that matches their clinical needs and their biological reality.

Kidney News: **You helped lead a discussion about trajectories of kidney diseases in children versus adults. What were some of the takeaways from that discussion?**

Trachtman: During a session that I moderated with Mona Khurana, MD, a pediatric nephrologist from the FDA, presentations by Carla Nester, MD, from the University of Iowa and Robert Nelson, MD, PhD, from the National Institute of Diabetes and Digestive and Kidney Diseases highlighted considerable similarity in the disease trajectories in pediatric and adult patients, both with diabetic and non-diabetic CKD. There were also differences and similarities in risk factors such as hypertension and levels of proteinuria and glomerular filtration rate at the time of diagnosis. Overall, the data documented some overlap between the diseases in children and adults but need to be explored in greater detail. The impact of diabetic nephropathy is profound in the pediatric population because those with type 2 diabetes in the pediatric age range are more likely to develop proteinuria compared with those with later-onset diabetes. There also were factors, such as exposure to maternal diabetes during pregnancy, that accelerated the development of diabetes in children, but the effect on the occurrence of kidney diseases was unclear.

Kidney News: **The workshop also addressed potential clinical trial designs for the pediatric population. Can you share more about that?**

Trachtman: The overarching theme of the workshop was the use of extrapolation by the FDA. We framed the discussion in an attempt to promote collaboration among all stakeholders and leverage what we know in the adult population. One of the key issues in extrapolation is determining which pediatric populations are distinct from adult counterparts and which need to be studied. While some diseases have considerable similarity to the adult population, such as focal segmental glomerulosclerosis and immunoglobulin A nephropathy, others are more distinctly pediatric in nature. For example, there is a large group of pediatric patients born with congenital anomalies of the kidney and the urinary tract who do not have a precise adult analog. We may be limited in what we can learn from adults in these cases.

Thus, for clinical trial designs, we must assess which pediatric populations need to be studied and for which populations we can leverage data that are available in adults to shed light on the applicability of drugs in children. Endpoints are important. Although the trajectory of disease may be similar, it does not mean that children will reach the endpoints classically used in clinical trial designs for adults with the same frequency that would allow trials to be conducted with comparable sample sizes and follow-up time. Regarding safety, we have the off-label experience with these drugs in pediatric patients with various conditions and clinical trial data for type 2 diabetes. Notably, before the meeting was convened, the FDA approved empagliflozin for adults with diabetes and for children with type 2 diabetes. The data were reassuring.

Kidney News: **Workshop attendees discussed several questions regarding CKD and the pharmacology of SGLT2 inhibitor drugs. What should our readers know?**

Trachtman: These drugs clearly are enormously beneficial in the adult population. There was a genuine sense of urgency to get these trials done in pediatrics before the therapeutic "cat is out of the bag," and we lose the opportunity as a community to systematically study them in pediatric patients. A key strength of the meeting was the sense of collegiality and shared enterprise among the stakeholders. There were patient advocacy groups, patient representatives, leaders from the FDA, representatives from industry, and, of course, nephrologists. It created a genuine sense of purpose and the need to keep the foot to the pedal. Hopefully, we can channel the momentum from the meeting to move forward and try to develop a clinical trial plan for SGLT2 inhibitors in pediatric CKD that is feasible and that would provide meaningful answers to nephrologists.

Kidney News: **What are the next steps for your group?**

Trachtman: The workshop was the first of a three-pronged effort. Following up from the workshop, we plan to create proceedings of the meeting that are publicly accessible and identify a mechanism to reconvene the group. Once reconvened, we need to identify steps to draft, design, and implement clinical trials that can be done in a timely, cost-effective manner and that answer the critical question: Is this class of drugs safe and effective in targeting the rate of progression of CKD in pediatric patients comparable with what has been observed in adults?

The second prong was the Annual KHI Stakeholders Meeting, held September 6–7, at which nephrologists discussed how they would make trials palatable to patients and care practitioners. The third prong will take place at Kidney Week in Philadelphia, PA, featuring a session (on Thursday, November 2, from 2 to 4 PM) coordinated with assistance from the KHI on "Clinical Trials in Pediatric CKD: Trial with SGLT2 Inhibitors?" William E. Smoyer, MD, vice president for clinical and translational research at Nationwide Children's Hospital, will present on "Designing Trials in Pediatric CKD: Hurdles and Solutions" during the session.

If successful in our goals, we will demonstrate that the pediatric nephrology community can work effectively to execute meaningful clinical trials that clarify the best way to treat the full range of pediatric patients with CKD. Long term, this multipronged approach could provide a model for tackling other urgent problems within pediatric nephrology. ■