Perspectives on Drug Development in Early ADPKD

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Introduction

The Critical Path Institute's Polycystic Disease Outcomes Consortium, including key stakeholders (patients, medical experts, industry experts, and regulators), held a PKD Regulatory Summit in May 2021. We highlight Session 2: Advancing Drug Development for Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Current Autosomal Dominant Polycystic Kidney Disease Therapy: Restricted to Adults at Risk of Rapid Progression

Diet and lifestyle clearly contribute to the risk of progression. Obesity, higher salt intake, and lower potassium intake have been linked to increased cyst growth. High water intake (1) has been suggested, but a water prescription study did not show benefit (2). Metabolic reprogramming is an important new field of study in ADPKD, and it may be that reduced caloric intake and intermittent fasting will prove to be beneficial strategies in the future.

Tolvaptan is indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD. Data regarding tolvaptan in children with ADPKD (NCT02964273) should be available soon.

Similar but varying standards for "rapidly progressing" have been adopted internationally (3). Older patients or those with smaller kidneys may still develop kidney failure but not meet the "rapidly progressing" standard. The efficacy of tolvaptan compares favorably with other renoprotective therapies (4); however, aquaretic side effects and frequent monitoring for liver injury limit full acceptance.

Prior drug approval processes were discussed. The Food and Drug Administration (FDA) agreed that a drug with a large treatment effect might be approved without labeling restrictions as there is a clear unmet need for drugs with greater therapeutic efficacy for all patients at risk of kidney failure, including those at lower risk of early progression.

Patient Selection for Trials: Risk, Monitoring, and Progression

Research is needed to define novel targets and the best timing for interventions relevant in the early disease stage before destruction of kidney parenchyma and loss of function (Figure 1) (5). These patients with ADPKD represent a crucial target for disease management. Challenges include the identification and validation of indicators, both measuring and predicting disease progression from childhood, and distinguishing slow from rapid progressors in this early-stage population.

In children, risk prediction tools are lacking. The onset of hypertension may be an important sign of high risk in this population. The ADPedKD registry (https://www.adpedkd.org/index.php?id=about) will establish the largest phenotyped pediatric ADPKD cohort, allowing for the development of risk stratification (5). ADPedKD is a global study including retrospective and prospective longitudinal data, providing the basis for the development of unified diagnostic, follow-up, and treatment practices.

A novel three-dimensional ultrasound method to measure the height-adjusted total kidney volume (htTKV) in children has been published (5). Three-dimensional ultrasound manual contouring volumetry outperformed the two-dimensional ultrasound ellipsoid method and was comparable with MRI volumetry in children, especially for smaller kidneys.

In adults, an average kidney length of 16.5 cm in a patient younger than 45 years is a good predictor of risk of early loss of kidney function (3). htTKV in combination with patient age and eGFR has been accepted as a prognostic biomarker by the FDA and European Medicines Agency (6).

htTKV does not fully predict the risk of progression for an individual patient as progression is sometimes nonlinear (7). Texture analysis (3) or quantification of variations in surface intensity of an image in addition to age, eGFR, and htTKV may provide better risk prediction.

Urine-plasma urea ratio reflects concentrating capacity, with lower ratios associating with rapidly progressive disease (8). Urinary monocyte chemoattractant protein-1, microRNAs, proteins in urinary exosomes, copeptin, and soluble urokinase plasminogen activator receptor levels may represent novel biomarkers.

PROPKD, a risk assessment using genotype, sex, early hypertension, or a urologic event (9), has high specificity but low sensitivity as occurrence of a urologic event before the age of 35 may be rare. Genotype may work best as part of a composite predictor tool (8).

Formal regulatory biomarker qualification procedures are useful to ensure regulatory acceptance of promising novel end points for the development of new drugs (6).

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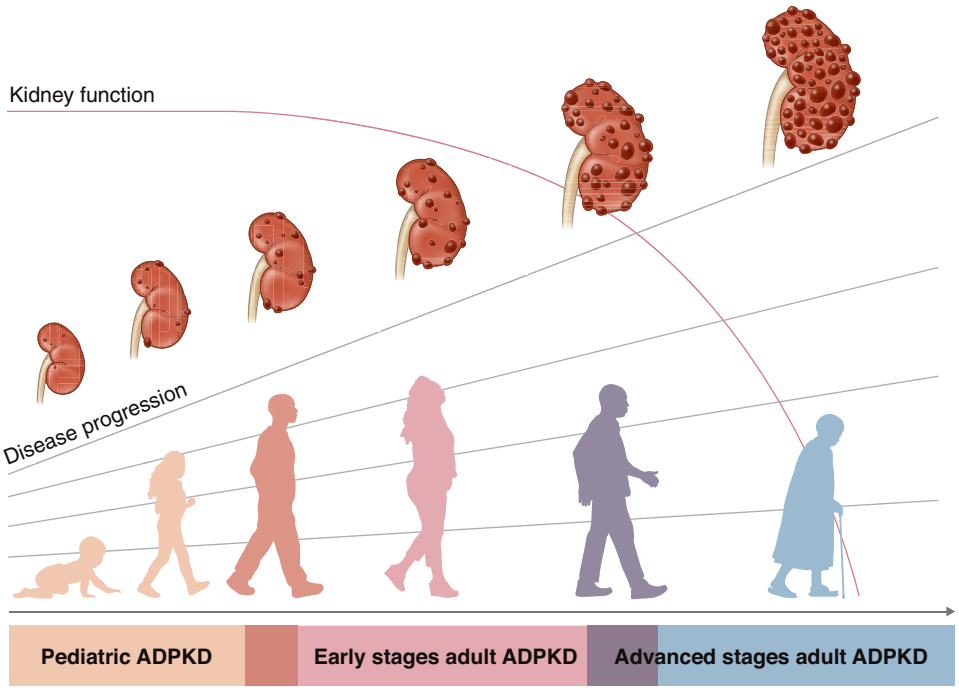

Patient stratification	• Very early onset, genetics, hypertension • No available stratification scores	• Age, genetics, urological events, hypertension • Stratification according to Mayo classification/PRO-PKD score	
Current primary end points	• Urine osmolarity	• HtTKV • eGFR	• eGFR • HtTKV
Current secondary end points	• HtTKV • eGFR	• Urine osmolarity • Number of cysts • Copeptin	• Copeptin • Liver cysts
Potential end points	• Texture/segmentation imaging • Number of cysts • Hypertension • uMCP1 • PRO	• Texture/segmentation imaging/ liver cysts • uMCP1/uEGF/suPAR/Kim-1/ β2 microglobulin/NGAL/ FGF23 • Urine-to-plasma urea ratio • PRO/pain	• PRO/pain/QoL • Liver cysts
Future directions	• "Bridging biomarkers": proteomic PKD score, microRNAs, and proteins in urinary extracellular vesicles		• Prediction modeling

Figure 1. | Published study end points for patients with autosomal dominant polycystic kidney disease (ADPKD) include height-adjusted total kidney volume (htTKV) and eGFR in adults and urinary osmolality in children. As GFR remains stable for years, other progression markers are needed for future clinical trials. Mayo classification (1A–1E) and/or the Predicting Renal Outcomes in Polycystic Kidney Disease (PRO-PKD) tool may be used for stratifying patients for selection in trials. Copeptin, kidney cyst number, and liver cysts are secondary end points used in previous studies, but all are not validated. Urinary monocyte chemoattractant protein-1 (uMCP1), kidney injury molecule-1 (Kim-1), β2-microglobulin, neutrophil gelatinase–associated lipocalin (NGAL), fibroblast growth factor 23 (FGF23), urinary epidermal growth factor (uEGF), soluble urokinase plasminogen activator receptor (suPAR), urine-plasma urea ratio, and patient-reported outcomes (PROs), such as pain, are potential biomarkers. Future directions in ADPKD including "bridging biomarkers," such as microRNAs, proteomics, and proteins in urinary extracellular vesicles, are promising. Automatic segmentation using artificial intelligence/machine learning may further enhance the interpretation of kidney growth, and number and size of cysts. Combining all of these efforts will lead to the development of prediction modeling with a more precise disease progression stratification. PKD, polycystic kidney disease; QoL, quality of life.

Extrarenal Manifestations: An Area of Opportunity

ADPKD is a multiorgan disorder. Liver cysts are the most common nonkidney finding, with premenopausal women over-represented as having severe hepatomegaly (10). Patient-reported symptoms increase with larger liver size, with a worse physical component score of quality of life (10). Surgical treatment includes cyst aspiration and sclerosis, fenestration, partial hepatectomy, or liver transplantation

(1). Medical treatment includes the use of long-acting octreotide analogs, which is a last resort therapy for patients who are not surgical candidates.

Intracerebral aneurysms are more common and occur at an earlier age in patients with ADPKD compared with unaffected individuals. The prevalence is about 3% in the general population and three-fold higher in ADPKD. The risk of intracerebral aneurysm is 11% in ADPKD without a family history and 23% with a family history (1).

Patient Perspective

Early treatment before significant kidney damage should be a priority. End points that substitute for eGFR as a key clinical outcome and other biomarkers of progression are lacking. A recent Delphi survey of patients, caregivers, and health care professionals found that prioritized outcomes were kidney function, kidney failure, death, blood pressure, kidney growth, and cerebral aneurysm. Kidney pain was the highest-rated patient-reported outcome (PRO) (11). Pain was also found to be a significant PRO in the PKD Foundation registry.

Although not all patients with ADPKD experience pain to the same degree, it can be the most significant burden in the lives of patients who experience it.

Future Directions

Current therapies under development include Bardoxolone (FALCON/Reata), GLPG-2737 (Galapagos), and miR-17 inhibition (Regulus). Eligible patients were at high risk of progression (younger, higher Mayo imaging class, and/or some loss of kidney function). Patients with lower Mayo imaging classification who may develop kidney failure in later life or patients at highest risk with preserved eGFR are excluded from current trials. Other unmet needs include therapy targeting both liver and kidney cysts, and therapy directed at pain.

PRO measures such as pain and disease-related interference with activities of daily living were thought to be critical for future trials. The value of PROs should be strengthened by clinician- and/or observer-reported outcomes, where applicable.

Outcome measures, including composite outcomes, were considered. eGFR is a poor outcome measure for high-risk patients early in their disease course who are unlikely to have significant change in eGFR during a typical study duration. The need for better biomarkers of progression was discussed extensively. In 2016, baseline total kidney volume in combination with patient age and baseline eGFR qualified as a prognostic enrichment biomarker for ADPKD in patients at high risk of 30% decline in kidney function (6). htTKV has been accepted as a reasonably likely surrogate for accelerated but not full approval (6).

Effectiveness of a drug in adults can provide evidence in support of efficacy in pediatric patients (*i.e.*, extrapolation of efficacy) if (*1*) the disease course is similar in adult and pediatric patients and (*2*) the response to the drug is similar in adult and pediatric patients. Assuming that these criteria are met, a biomarker pertinent to disease pathophysiology and the mechanism of action of the drug, which correlates with clinical outcomes in adult and pediatric patients with ADPKD, could be used to evaluate or "bridge" the efficacy of a specific drug in adults to pediatric patients with ADPKD (*i.e.*, using a "bridging biomarker" approach).

Future studies targeting kidney-based efficacy end points should assess the effects on extrarenal disease manifestations as part of safety assessments (*e.g.*, effects on the liver) and *vice versa*. The potential risks and benefits of composite kidney and liver efficacy end points were considered.

Disclosures

N.K. Dahl serves as a principal investigator for clinical trials sponsored by Allena, Kadmon, Reata, Regulus, and Sanofi; serves on the unbranded speakers bureau for Otsuka; reports consultancy agreements with Otsuka Pharmaceutical and Vertex; reports honoraria from AstraZeneca, the National Kidney Foundation, and Otsuka Pharmaceutical; reports advisory or leadership roles for the Natera Scientific Advisory Board and the PKD Foundation; and reports other interests or relationships with the Medical Advisory Board of the National Kidney Foundation serving Connecticut Chapter. D. Mekahli serves on advisory boards for Otsuka Pharmaceutical, Reata, and Sanofi Genzyme as a representative of the University Hospital of Leuven and has received educational grants from Otsuka Pharmaceutical paid to the University Hospital of Leuven, all outside the submitted work. The remaining author has nothing to disclose.

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Author Contributions

N.K. Dahl and D. Mekahli conceptualized the study; N.K. Dahl, D. Mekahli, and H. Womack wrote the original draft; and N.K. Dahl and D. Mekahli reviewed and edited the manuscript.

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