Emerging Therapies in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder and a leading monogenic cause of kidney failure. Reduction or loss of polycystin-1 (PC1) and polycystin-2 (PC2) function disrupts ciliary calcium signaling, elevates cyclic AMP (cAMP), reprograms cellular metabolism, and activates proliferative cascades that drive cyst expansion. Tolvaptan, a vasopressin V2 receptor antagonist, established cAMP modulation as a disease-modifying strategy but is limited by aquaretic effects and hepatotoxicity risk. This review highlights emerging therapeutic strategies in clinical trial development that extend beyond vasopressin antagonism. Gene-directed therapies aim to restore polycystin dosage, including anti-miR-17 oligonucleotides (e.g., farabursen) and pharmacochaperones that rescue misfolded PC1 and restore trafficking in select PKD1 missense variants (e.g., VX-407). Paracrine signaling can be modulated with anti-pregnancy-associated plasma protein A (PAPP-A) antibodies that reduce insulin-like growth factor-1 (IGF-1) bioavailability in cystic microenvironments. Metabolic reprogramming is targeted by agents such as metformin, bempedoic acid, GLP-1 receptor agonists, and structured dietary interventions. Sodium-glucose cotransporter 2 (SGLT2) inhibitors hold theoretical promise but await definitive results from ongoing trials. A novel cAMP-lowering strategy via phosphodiesterase-4 (PDE4) activation is advancing toward clinical testing. Looking ahead, gene therapy and genome editing offer the potential to raise polycystin levels above the threshold for cystogenesis, although challenges in vector capacity, kidney-specific delivery, and durability remain. Artificial intelligence (AI)-guided discovery, coupled with human organoid platforms, is accelerating therapeutic repurposing and rational combination design. Collectively, these advances signal a transition toward a layered, mechanism-guided framework in which vasopressin blockade is integrated with metabolic, other signaling, and genotype-specific therapies. As biomarkers and risk stratification tools mature, ADPKD management is poised to become increasingly precise, tolerable, and effective.

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