Kidney Medicine Review

Advances in Autosomal Dominant Polycystic Kidney Disease: A Clinical Review

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Polycystic kidney disease (PKD) is a multiorgan disorder resulting in fluid-filled cyst formation in the kidneys and other systems. The replacement of kidney parenchyma with an ever-increasing volume of cysts eventually leads to kidney failure. Recently, increased understanding of the pathophysiology of PKD and genetic advances have led to new approaches of treatment targeting physiologic pathways, which has been proven to slow the progression of certain types of the disease. We review the pathophysiologic patterns and recent advances in the clinical pharmacotherapy of autosomal dominant PKD. A multipronged approach with pharmacologic and nonpharmacologic treatments can be successfully used to slow down the rate of progression of autosomal dominant PKD to kidney failure.

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PREVALENCE

The most common kidney disease displaying Mendelian inheritance is autosomal dominant polycystic kidney disease (ADPKD). The incidence has been observed to be 1 in 500 to 1 in 1,000 people.[1] There are 600,000 patients with ADPKD in the United States and 12 million patients with ADPKD globally.[2] About 7 in 10 patients with ADPKD progress to kidney failure, with patients starting dialysis in the latter half of the fifth decade of life (median age of 58 years).[3] ADPKD is the fourth leading cause of kidney failure in the United States[4] and worldwide.[5]

Men have higher rates of progression to kidney failure in the United States than women (8.2 compared to 6.8 per million).[5] The observed trend toward later average age of transition to kidney failure in patients with ADPKD is hypothesized to be due to reduced cardiovascular mortality of older patients with ADPKD. These patients now survive long enough to experience kidney failure, whereas in the past they would die of cardiovascular complications that they were at increased risk for due to chronic kidney disease (CKD).[5]

GENETICS AND PATHOPHYSIOLOGY

In ADPKD, kidney parenchyma is gradually displaced by progressive growth of kidney cysts in both kidneys. This results in interruption of the filtration and physiologic functions of the kidneys (Box 1).[6] The surviving glomeruli hypertrophy and perform compensatory hyperfiltration, which maintains kidney function within a relatively normal range for decades.[7] Kidney function decline only manifests after kidney reserve has been exhausted and a large portion of nephrons have been replaced by cystic tissue. Typically, kidney failure eventually develops after the fourth decade of life in ADPKD.[8]

Polycystin 1 (PC1) is the protein product of the PKD1 gene and PC2 is the protein product of the PKD2 gene. PKD1 is responsible for 85% of ADPKD cases, while PKD2 is responsible for 15% of ADPKD cases (Fig 1).[9]

The PKD1 gene is located on chromosome 16p13.3, while the PKD2 gene is located on chromosome 4q22. Other mutations that have been found in patients with ADPKD during recent clinical trials are GANAB (which causes a mild cystic disease that does not progress to kidney failure) and DNAJB11 (which causes a type of cystic disease in which kidney failure may develop without marked kidney enlargement).[10,11]

Compared with *PKD1*, individuals affected with *PKD2* mutations have milder kidney disease with fewer kidney cysts, delayed onset of hypertension and kidney failure, and longer patient survival.[8] However, identical renal and extrarenal manifestations are seen in patients with both mutations[12] (Table 1[13]). In ADPKD, cysts can arise from any tubular segment, sprout from the nephron, and no longer communicate with the tubule from which they originate. The majority of cysts still accumulate fluid within the lumen after they are disconnected from tubular structures.[14]

In 10% to 15% of patients with ADPKD, there is no positive family history for the disease, which can be explained by de novo mutations or failure to diagnose cystic kidney disease in mildly affected family members.[12,15]

A recent study using whole-exome sequencing and long-range polymerase chain reaction techniques involved renal epithelial cells of 9 patients with ADPKD with *PKD1* and *PKD2* gene mutations.[16] Somatic mutations of *PKD1* or *PKD2* were identified in all patients and in 90% of the cysts analyzed; 90% of these mutations were truncating, splice site, or in-frame variations predicted to be pathogenic mutations.[16] In another study of PKD1 knockout mice, it was suggested that monocyte chemoattractant protein-1 (Mcp1) upregulation promotes macrophage accumulation and cyst growth through both proliferation-independent and proliferation-dependent mechanisms in this corresponding mouse model of ADPKD.[17]

Box 1. How ADPKD Affects the Kidneys

1. Hypertension
2. Acute and chronic pain
3. Cyst and urinary tract infections
4. Hematuria
5. Kidney stones
6. Urine concentration defects
7. Loss of kidney function

Abbreviation: ADPKD, autosomal dominant polycystic kidney disease.

Table 1. Genetic Mutations in ADPKD

Mutation Type	PKD1	PKD2	Overall
Frameshift deletion/insertion	32%	25.9%	31.1%
Nonsense	26.5%	11.1%	24.4%
Splicing	10.5%	22.2%	12.2%
Missense	24.8%	33.3%	26.1%
In frame deletion/insertion	5.9%	7.4%	6.1%

Abbreviation: ADPKD, autosomal dominant polycystic kidney disease.
Data from Rossetti et al.[13]

Polycystins and Ciliopathy

Polycystins are expressed in renal tubular epithelia, hepatic bile ducts, and pancreatic ducts. They are a subfamily of protein channels that are involved as regulators of intracellular calcium signaling. PC1 is located in tight junctions and primary cilia and has function in regulating cell-to-cell contacts. PC1's probable function is as an adhesion molecule or possibly a receptor. PC2 is a calcium-permeable nonselective cation channel that localizes to primary cilia and endoplasmic reticulum and has been reportedly isolated in the plasma membrane. These proteins form the PC complex, which plays a role in intracellular calcium regulation within the primary cilia and other organelles.[5]

Calcium and Cyclic Adenosine Monophosphate Signaling

The protein products of *PKD1* and *PKD2* are involved in establishing planar cell polarity, which is an important organizer of organogenesis in embryonic development.[18] Vasopressin sensitivity and its physiologic effect of urinary concentration is mediated by a loss of local intracellular calcium leads and a resulting increase in cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA). The loss of calcium's inhibitory effect on cAMP signaling activates extracellular signal-regulated kinase (ERK) signaling, Wnt-β-catenin, signal transducer and activator of transcription 3 (STAT3), and possibly PAX2 signaling. This occurs through the phosphorylation of PKA, B-Raf, and mitogen activated protein kinase

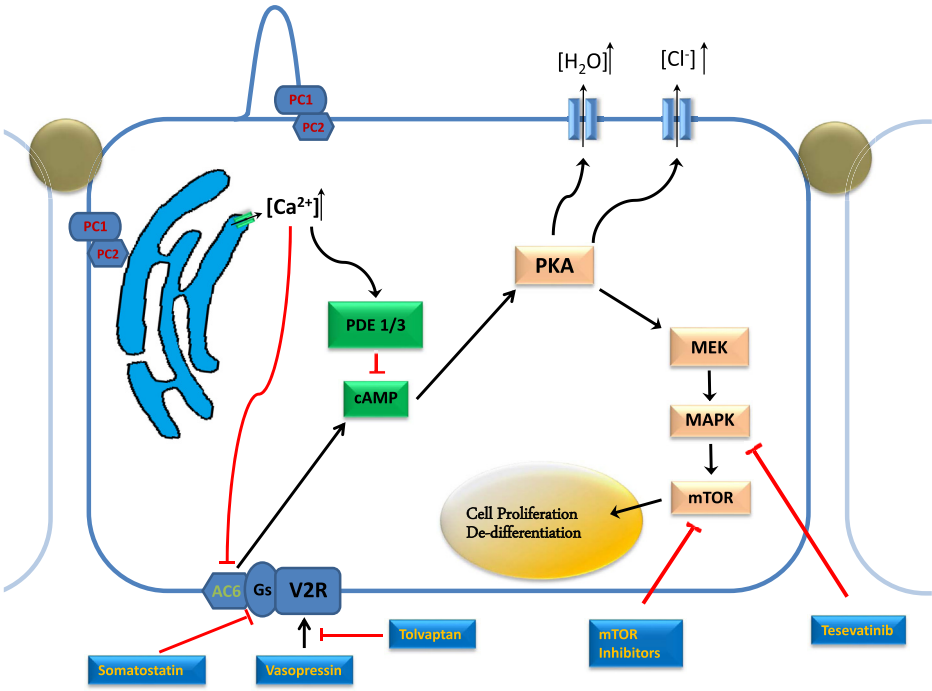

Figure 1. Pathophysiology and genetics of autosomal dominant polycystic kidney disease (ADPKD) show the multiple abnormal signaling pathways. Abbreviations: AC6, adenylate cyclase 6; Ca^{2+}, calcium ions; cAMP, cyclic adenosine monophosphate; Cl^{-}, chloride ions; Gs, g protein; H_20, water molecules (entry via aquaporins); MAPK, mitogen activated protein kinase; MEK, dual threonine and tyrosine recognition kinase; mTOR, mammalian target of rapamycin; PC1, polycystin 1; PC2, polycystin 2; PDE1, phosphodiesterase 1; PDE3, phosphodiesterase 3; PKA, protein kinase A; V2R, vasopressin 2 receptor.

(MAPK) kinases in a sequential manner.[19,20] The result of activation of the PKA of the mentioned cell-cycle mediator proteins is impaired tubulogenesis, cell proliferation, increased fluid secretion, and interstitial inflammation. The cAMP-dependent transporter encoded by the *CFTR* gene is also affected and abnormal epithelial secretion of chloride then results. This abnormal anion is also thought to play an important role in the generation and persistence of the fluid-filled cysts in ADPKD.[21]

Vasopressin

From 2010 onward, studies have identified that circulating serum vasopressin acting on V2 receptors (V2Rs) in the basolateral membranes and urinary vasopressin acting on the primary cilia modulate the pathogenesis of polycystic kidney disease (PKD).[22] The newly developed V2R agonists presented a natural target that would thwart the pathogenesis of this disease by increasing cAMP levels in kidney cells and arresting cyst development. This has been confirmed in murine models of autosomal recessive PKD (PCK rat) and ADPKD caused by *PKD1* ($Pkd1^{RC/RC}$ mouse) or *PKD2* ($Pkd2^{WS25/-}$ mouse) mutations.[23] Given decreased urinary concentration in ADPKD, vasopressin resistant and commensurately high vasopressin levels were observed in patients with ADPKD at baseline and despite attempts at suppression of the hormone with 3% saline solution infusion.[24] The peripheral resistance was thought to be due to loss of the interstitial osmotic gradient that drives water reabsorption in the cortical collecting duct mediated by the cystic lesions of PKD. This would inhibit normal feedback signaling, resulting in a high level of near-constitutive vasopressin expression.[25] Consistent with these observations, patients with ADPKD with intact glomerular filtration rates (GFRs) had defective vasopressin response to the normal stimulus of reduced plasma osmolality as compared with non-PKD control patients.[26]

Mammalian Target of Rapamycin Signaling

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase. It is involved intimately in cell growth/proliferation, protein synthesis, cellular metabolism control, and transcription control.[27] Polycystins interact with and partly regulate the mTOR pathway, and there is increased mTOR signaling observed in PKD.[28]

PC1 interacts with the protein products of the *TSC1* and *TSC2* genes, these proteins form a complex with mTOR kinase, and are required for proper cellular signaling.[27] PC1 stabilizes the TSC1/TSC2 complex, thus suppressing mTOR activity and explaining the increased mTOR signaling in PKD, which occurs due to the loss of PC1's inhibitory function on the mTOR pathway.[29] In *pkd1* mutant mice, *mTOR* and its downstream effector S6 kinase were seen in cyst-lining epithelial cells.[27] This confirms the molecular theory suggesting that loss of PC1 results in loss of inhibitory activity, increased mTOR activity, and cyst formation. PC1 inhibits mTOR activity by interacting with tuberin and preventing tuberin's inactivation through phosphorylation by ERK and Akt kinases.[30] The increased level of tuberin binds mTOR and results in inactivation of the mTOR complex. The powerful role of mTOR activation results in cystcl stimulation, and proliferation was suggested by the rapid rate of cystogenesis in patients carrying deletions of PKD1 and its adjacent gene TSC.[28]

Epidermal Growth Factor Receptor Signaling

There are 4 transmembrane receptors in the epidermal growth factor receptor gene family. Epidermal growth factor receptor has been linked to abnormal cyst formation in vitro and in vivo, suggesting a role in PKD. Because the polarity of cells is disturbed in PKD, the basolateral location of the epidermal growth factor receptor is reversed, resulting in aberrant expression of the receptor on the apical surface of the cyst epithelium.[31]

Epidermal growth factor is an important mediator of the proliferative abnormality seen in cyst formation in human and mouse models of ADPKD.[14] Epidermal growth factor is a small mitogenic protein that is involved in mechanisms such as cellular proliferation and fluid secretion and plays an important role in the expansion of kidney cysts.[32] Epithelial cells from cysts from patients with ADPKD are unusually susceptible to the proliferative stimulus of epidermal growth factor.[14]

Sequential activation of PKC/AKT, PLCγ, dual threonine and tyrosine recognition kinase (MEK)/Erk, or c-Src by epidermal growth factor receptor is thought to lead to ADPKD cell proliferation.[19,32] ERKs can also be activated by increased cAMP levels due to the epidermal growth factor receptor signal.[9] Transforming growth factor α (TGF-α) expression may be abnormally upregulated, and cells with TGF-α overexpression have displayed abnormal kidney cyst development.[33] Epidermal growth factor receptors and soluble ligands for these receptors produced by PKD cyst epithelia create a positive feedback cycle of autocrine-paracrine stimulation that results in runaway proliferation cysts in ADPKD.[34]

DIAGNOSIS

ADPKD is diagnosed on the basis of imaging. Given the low cost, safety, and availability of ultrasonography, it is a logical first choice for confirming a suspected ADPKD diagnosis. There are useful age-dependent ultrasound criteria for both diagnosis and disease exclusion when a family history of ADPKD has been established.[35] In probands with PKD1 and PKD2 family history, the diagnosis is established by the presence of 3 or more kidney cysts (unilateral or bilateral) for at-risk individuals 15 to 39 years old, 2 (≥2 cysts in each kidney) for individuals 40 to 59 years old, and 8 (≥4 cysts in each) for individuals 60 years or older.[36] If the genotype is unknown, the presence of at least 3 (unilateral or bilateral) kidney cysts, 2 cysts in each kidney, and 4 or more cysts in each kidney

can be regarded as sufficient for the diagnosis of at-risk individuals aged 15 to 39, 40 to 59, and 60 years or older, respectively.[36] Magnetic resonance imaging (MRI) and high-resolution ultrasound represent more advanced imaging techniques that may help with disease exclusion in at-risk individuals.[37]

Genetic testing is not done as part of standard care because of the technical challenges of analyzing PKD1 and clearly established criteria of imaging diagnostics.[38] Exceptional patients who need genetic testing include potential living related kidney donors with negative or equivocal scans[39] and very early-onset cases in neonates (because of the high recurrence rate [45%] for subsequent pregnancies[40]). Because ADPKD can present as a new mutation, atypical presentations, especially in patients with a negative family history (6%-8% are de novo mutations) may benefit from genetic testing and counseling.

It is possible that genetic testing will find a larger forum if genetic data can help predict who will respond to the therapeutic advancements that tolvaptan antagonist treatment may bring to ADPKD pharmacotherapy.[40] Next-generation sequencing panel examination is the preferred mode of testing, rather than single ADPKD gene allele identification. This is because of phenotypic overlap between different cystic kidney diseases and genetic heterogeneity.[41] The panel for cystic kidney disease should adequately contain coverage of *PKD1*, *PKD2*, *PKHD1*, *HNF1B*, and genes for other ciliopathies.[42]

KIDNEY MANIFESTATIONS OF ADPKD

Pain is one of the most common manifestations in patients with ADPKD, occurs early in the course of the disease, and often leads to the diagnosis. Pain presentation in ADPKD could be of an acute pattern as in nephrolithiasis, urinary tract infection, cyst infection, or hemorrhage or it could be more of a chronic disabling pattern.[43] Patients with ADPKD report radicular pain located in the low back, abdomen, chest, and legs. Pain patterns rely on renal sympathetic, parasympathetic, and sensory innervation. Extensive cross-connection with innervation to other organs explains the complexity of referred pain in some patients.[43]

Cyst complications include cyst infections and acute pyelonephritis with symptoms such as fever, leukocytosis, and flank pain. Urine for Gram stain and culture should be immediately obtained and appropriate antibiotic management quickly started, though urine culture is not always positive.[43] Rupture of an infected cyst is associated with extravasation into the retroperitoneal space and the patient presents with symptoms of peritonitis such as fever, vomiting, and abdominal pain or tenderness. The pain may be initially localized to the flank, but it becomes diffuse if the infection is not controlled.[44] Cystic hemorrhage frequently occurs in patients with ADPKD and clinically manifests as gross hematuria and passage of clots, sharp localized abdominal pain, and perirenal hematoma.[45] Vascular endothelial growth factor (VEGF) produced by the cystic epithelium promotes angiogenesis, which increases the risk for cystic hemorrhage.[46]

Nephrolithiasis is one of the important clinical features of ADPKD and it occurs as high as twice in patients with ADPKD compared with the general population; 10% to 35% of patients with ADPKD are reported to have nephrolithiasis,[47] and it should always be considered as a probable cause of flank pain in these patients. The increased incidence of kidney stone formation in patients with ADPKD can be explained by low urine levels of inhibitors of stone formation such as citrate, as well as increased intrarenal anatomic obstruction.[48] Half the patients with ADPKD with kidney stones have symptoms that include pain, obstruction, hematuria, and urinary tract infection exacerbation.[49] Computed tomography is the most sensitive imaging technique for the evaluation of nephrolithiasis and calcifications in patients with ADPKD.[47] The management plan includes correction of electrolyte disturbance, treatment of any coexisting urinary tract infection, urgent relief of obstructions, and accurate selection of the endourologic procedure.[50]

PROGRESSION

Classic laboratory monitoring of APKD includes serum creatinine levels and estimated GFR (eGFR) testing. These tests are very limited early in disease progression due to the high level of kidney reserve that can mask kidney parenchymal damage. This is confirmed by the observation that serum creatinine level usually does not increase for 3 to 5 decades, and only then is there an observable loss of kidney function.[51] Total kidney volume (TKV) is a practical and pathogenically linked marker that can be practically measured in ADPKD.[51] TKV has proved to be a useful biomarker in ADPKD clinical trials, and it boasts higher sensitivity for disease progression than GFR or serum creatinine level.[52]

The US Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP) has identified increases in kidney size as the earliest manifestation of PKD.[53] The CRISP study showed that increases in TKV correlate with increased cyst volume and a decrease in GFR.[52] A baseline height-adjusted TKV (htTKV) increase of 100 mL/m significantly predicted CKD stage 3 development within 8 years by multivariate regression analysis with a 1.48 odds ratio (95% confidence interval, 1.29-1.70). MRI determination of baseline htTKV > 600 mL/m predicted CKD stage 3 development within 8 years. Area under the curve for this measurement was 0.84 (95% confidence interval, 0.79-0.90). This is the basis of using htTKV as a prognostic biomarker in patients with ADPKD.[54]

The CRISP study found that higher TKV is associated with proteinuria, microalbuminuria, hypertension, gross hematuria, and progressive loss of kidney function.[51] Kidney length measurement by ultrasound also predicted GFR decline in cohorts of patients in a research setting.

Box 2. Risk Factors for Rapid ADPKD Progression

1. *PKD1* mutations (truncating mutations have the worst outlook)
2. Age and early decrease in eGFR (onset of kidney failure at age <55 y, development of stage 3 CKD at <40 y)[56]
3. Male sex
4. Confirmed eGFR decline ≥ 5 mL/min/1.73 m^2 in 1 y or ≥2.5 mL/min/1.73 m^2 per y over a period of 5 y[57]
5. Early onset of hypertension
6. High TKV (Mayo classification 1C-1E)
7. Early onset or repeated episodes of gross hematuria
8. Hypertensive women with ≥3 pregnancies had significantly worse kidney function than age-adjusted women with fewer pregnancies[56]
9. Proteinuria, microalbuminuria, and elevated serum copeptin levels
10. Obesity

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TKV, total kidney volume.

Given the relative inaccuracy and operator dependence of kidney length measurements, it is of limited utility for making clinical treatment decisions. Ultrasound measurements have been found to estimate true kidney size, especially in advanced ADPKD stages, and as mentioned, are operator dependent.[55] Risk factors for rapid ADPKD progression are noted in Box 2.[56,57]

TREATMENT AND MANAGEMENT OF PKD

Current treatment strategy of patients with ADPKD is stratified into 2 major categories: lifestyle measures and pharmacologic treatment.

Lifestyle Management of ADPKD

General Measures

Supportive measures aim to reduce morbidity and mortality associated with ADPKD disease manifestations.[8] These include strict blood pressure control (<110/75 mm Hg) and increased water consumption, which can decrease vasopressin levels[58] because vasopressin secretion is mainly controlled by serum osmolarity and consequently water intake. Therefore, it is recommended for patients with ADPKD to consume 3 to 3.5 L/d of water,[59] which has been shown sufficient to reach urine osmolarity < 280 mOsm/kg, which indicates suppression of vasopressin secretion.[60] Restriction of sodium intake to 2.3 to 3 g/d[61] is an essential supportive measure for patients with ADPKD. The importance of dietary salt restriction in ADPKD has received attention because persistent high salt intake stimulates vasopressin secretion, promotes plasma levels of endogenous cardiotonic steroids, and increases kidney production of TGF-β.[52] Additionally, patients with ADPKD are advised to avoid smoking, limit alcohol intake, and exercise.[8]

Hypertension

One of the most common complications of ADPKD is the development of hypertension. Before any noticeable decline in kidney function, 50% to 70% of ADPKD cases present with hypertension. The average age of development of hypertension in patients with ADPKD is 30 years.[5] The cause is multifactorial. Hypertensive patients with ADPKD show increased activation of the renin-angiotensin-aldosterone system (RAAS) compared with patients with essential hypertension of the same age, kidney function, and level of blood pressure.[62]

A trial that pointed to the importance of blood pressure control in PKD is the HALT-PKD study.[63] A combination of an angiotensin-converting enzyme inhibitor and an angiotensin II receptor subtype 1 blocker was given to 1,000 patients with ADPKD for 5.5 years. In the intervention arm targeting lower blood pressure (95/60-110/75 mm Hg), there was a delayed increase in TKV, along with decreased left ventricular hypertrophy and less proteinuria.[64]

Rigorous blood pressure control according to the HALT-PKD protocol diminished the annual rate of increase in TKV by 14.2%.[63] Patients with ADPKD with eGFRs ≥ 30 mL/min/1·73 m^2 tolerated dual RAAS blockade well.[40] The second arm of HALT-PKD (arm B) found that outcomes with single-agent blockade of the RAAS were equivalent to dual RAAS blockade. This suggests that dual RAAS blockade, which carries higher risk for hyperkalemia and changes in kidney function, is not necessary for optimal renoprotection in ADPKD.[65]

Kidney Transplantation

Prophylactic nephrectomy of patients with ADPKD undergoing transplantation is not routinely recommended due to associated increases in morbidity and mortality.[66] Kidney size typically declines after transplantation, and thus a nephrectomy may not be necessary after kidney transplantation (Box 3).[67] Patients with ADPKD have equivalent posttransplantation morbidity as other nondiabetic kidney transplant recipients.[68]

Management of Cerebral Aneurysms

Cerebral aneurysms are usually asymptomatic extrarenal manifestations in patients with ADPKD who have higher risk for intracranial aneurysm formation compared with the general population (8% vs 2%),[69,70] although the risk for rupture or bleeding is the same compared with the

Box 3. Indications for Nephrectomy Before Transplantation

1. Recurrent and/or severe infection
2. Symptomatic nephrolithiasis
3. Recurrent and/or severe bleeding
4. Intractable pain
5. Suspicion of kidney cancer and space restrictions

general population.[69] The risk for forming intracranial aneurysms cannot be related to the decline in kidney function because 50% of these patients have preserved kidney function.[71] Results of many studies recommend magnetic resonance angiography–based screening of all patients with ADPKD older than 30 years for intracranial aneurysms who have a family history of intracranial aneurysm with or without rupture.[72] The decision of selecting a conservative, endovascular, or surgical approach is decided on the size, site, and morphology of the aneurysm, as well as taking into consideration the age of the patient and other comorbid conditions.[73]

Pharmacologic Treatment of PKD

Until recently, all that could be offered to patients with ADPKD were supportive measures. This was during the era when there was a lack of targeted therapeutic strategies.[5] The landscape of pharmacotherapy changed with the approval of V2R blockade. This was an eagerly and urgently awaited advance for patients with ADPKD that seems to benefit patients with the most rapidly progressive disease.[74]

Tolvaptan (V2R antagonists)

There are multiple V2R antagonists that were first approved for the treatment of hypervolemic and euvolemic hyponatremia. One such agent is tolvaptan, which has demonstrated highly avid binding and affinity for the V2R. In binding this receptor, tolvaptan inhibits the ERK pathway, cAMP production, chloride secretion, and in vitro growth of cysts in 3-dimensionally cultured ADPKD cells.[75]

The pharmacokinetics of tolvaptan in adult patients with ADPKD has been examined, and its safety was confirmed.[76] Tolvaptan Phase 3 Efficacy and Safety Study in ADPKD (TEMPO 3:4) included 1,445 adult patients without reduced GFRs (>60 mL/min) and with enlarged kidneys (TKV > 750 mL, as measured using MRI). Tolvaptan was evaluated and the effect of treatment was assessed on the change in TKV and eGFR in comparison to placebo.[77] TEMPO demonstrated that V2 antagonism with tolvaptan delayed the rate of TKV growth by 45% (from 5.5% to 2.8% per year). Importantly, the rate of eGFR loss was reduced by 26% (from 3.70 to 2.72 mL/min/1.73 m^2 per year) during 3 years of follow-up.[78] A secondary outcome showed that there was 36% lower risk for patient-reported kidney pain.[79]

The REPRISE (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD) trial was a 12-month randomized with an 8-week prerandomization phase, multicenter, placebo-controlled, double-blind trial. The results of this landmark trial confirmed that tolvaptan slowed disease progression in ADPKD.[80,81] Tolvaptan contributed to a slower rate of kidney function decline as compared to placebo over a period of up to 12 months in patients with CKD stages 2 to 4 caused by ADPKD. Participants' eGFRs were 25 to 65 mL/min/1.73 m^2.[82] Mean decline in eGFR from baseline to 12 months was 35%.[78] In both REPRISE and TEMPO 3:4, tolvaptan had the greatest beneficial effect on eGFR decline in patients with baseline eGFRs > 45 mL/min/1.73 m^2 (CKD stage 3a).[79]

The following adverse events were reported in patients taking tolvaptan: polyuria, thirst, and nocturia. They were related to increased water intake and the polyuria caused by V2R antagonism. The study population reported fewer adverse events related to ADPKD: pain and urinary tract infection.[76,78,80] Patients treated with tolvaptan also showed an increase in serum sodium and uric acid levels and the frequency of gout, likely due to free-water loss and relative hemoconcentration.[78] It was also noted on review of the data that tolvaptan decreased albuminuria compared with placebo in a manner independent of blood pressure change.[83]

A limited number of patients developed liver enzyme level abnormalities thought to be due to hepatocellular injury; these enzyme level abnormalities resolved after discontinuation of treatment with the drug.[84] Given these findings, a risk evaluation and mitigation strategy involving frequent liver function testing before initiation and at specific intervals (after 2 and 4 weeks, then monthly for 18 months and every 3 months thereafter) is required for tolvaptan treatment in all patients with ADPKD.[57] The US Food and Drug Administration (FDA) mandates frequent monitoring of liver function test results after treatment initiation.[57] These risk evaluation and mitigation programs are available in the United States only. Using other drugs with tolvaptan, such as cytochrome P450, family 3, subfamily A inhibitors and diuretics, at the same time is not recommended, although some studies have suggested that a thiazide may reduce polyuria, increasing the tolerability of tolvaptan.[85,86] The need to train patients to drink water at the signs of thirst and keep up water intake to match aquaresis induced by tolvaptan is important. Although an extremely rare event, especially in normonatremic patients, tolvaptan has led to a rapid increase in serum sodium levels and in one case to osmotic demyelination syndrome.[72]

Tolvaptan's FDA-approved indication is to slow down kidney function decline in adults with rapidly progressive ADPKD (classes IC, ID, and IE especially).[57] The use of htTKV as a marker to predict disease progression was confirmed by the PKD Outcomes Consortium. Thus, htTKV, age, and GFR are now approved as prognostic markers for rapid progression of the disease.[87] These criteria should be used to identify individuals who have the highest risk for rapid progression. It is important to use imaging to determine the classification, as well as to rule out other contributing factors such as genetic mutations other than PC1 and PC2 gene mutations.[57]

The Mayo imaging classification calls for the use of computed tomography (including contrast enhancement in patients with eGFRs > 60 mL/min/1.73 m^2) or MRI without contrast (in patients with reduced eGFRs).[88,89] Imaging findings are also cross-referenced with age to

identify patients at risk for rapid progression who would benefit the most from pharmacotherapy.

Around 95% of patients with ADPKD have typical diffuse cystic disease (class 1), which is divided into 5 classes (A, B, C, D, and E) based on growth rates (<1.5%, 1.5%-3%, 3%-4.5%, 4.5%-6%, or >6% per year, respectively).[90] Patients in classes 1C, 1D, or 1E are the most likely to benefit from treatment, and the benefit is predicted to be greater in young patients.[80]

The Mayo classifications have not been validated in all ethnic or racial groups (nonwhite). The cost of imaging may partially limit full use of this classification system, though the cost concerns of imaging are likely to be minor compared with the cost of tolvaptan and concerns about liver safety requiring frequent laboratory testing.[57]

An alternative classification for ADPKD is the European Renal Association–European Dialysis and Transplant Association algorithm. Unlike the imaging-based Mayo imaging classification, this system emphasizes eGFR indexed for age.[91] This algorithm can distinguish rapidly from slowly progressive disease in the majority of patients with ADPKD. Its main limitations are in young patients aged 18 to 30 years.[57] However, the Mayo imaging classification has the advantage of having been validated in an independent clinical study.[90] This classification has also proved to be informative in post hoc analyses of several clinical trials.[92]

The predicting renal outcomes in ADPKD (PROPKD) score uses genetics, urologic complications, hypertension, and sex to create a model that predicts progression of the disease.[93] While it seems to be useful in patients older than 35 years, it has limited value in patients younger than 35 years who do not have complications or in patients who are missing clinical information. Genetic information alone can be used to determine prognosis for these patients.[94] Approximately 5% of patients with ADPKD present with class 2 (atypical) disease. In these cases, treatment with tolvaptan is not recommended. These patients are managed with monitoring and general measures such as strict blood pressure control, moderate sodium restriction, increased hydration, and maintaining normal body mass index.[57]

Statins

There are known antiproliferative, anti-inflammatory, and antioxidant effects of HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors. These effects have been demonstrated independently of cholesterol lowering.[95,96] Statin therapy was not demonstrated to be beneficial in the HALT-PKD trial.[97] However, another small trial of children and adolescents showed reduced kidney cyst growth in patients treated with pravastatin administration for 3 years.[98] Because KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend the use of statins for cardioprotection in all patients with CKD who are older than 50 years and not receiving dialysis, these drugs may serve a secondary role in patients with CKD with ADPKD of helping to prevent cyst growth.[99] Coadministration of tolvaptan and statins could increase the levels of organic anion transporter (OAT) P1B1/3 and OAT3 transporter substrates including statins, potentiating the statins effect.[57] Therefore, larger trials in adults are needed to determine the optimal role of statins in ADPKD management. Monitoring for rhabdomyolysis and myositis is also routinely done.

Other Experimental Agents

Tyrosine Kinase Inhibitors (tesevatinib). Tesevatinib is a tyrosine kinase inhibitor with demonstrated clinical activity against epidermal growth factor receptor.[73] Tesevatinib has potential antineoplastic activity.[74] Early clinical studies have shown that tesevatinib might reduce cyst growth in patients with ADPKD. A phase 1 study has been completed, demonstrating that tesevatinib was generally well tolerated. In vitro studies showed that tesevatinib potently inhibits MATE1/2-K transporters, which may explain mild serum creatinine level increases associated with tesevatinib treatment.

Preliminary data from the ongoing phase 2 clinical trial of tesevatinib for treatment of ADPKD reported corrected QT interval prolongation seen in 25% of patients treated with 100 mg/d. The most common reported adverse events were those associated with epidermal growth factor receptor kinase inhibition: diarrhea, nausea, and acneiform rash. These data suggest that tesevatinib may be a safe and effective therapy for childhood autosomal recessive PKD.[74]

Bosutinib is an oral dual Src/Bcr-Abl tyrosine kinase inhibitor that is approved for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia in patients resistant to imatinib.[75] In a recent phase 2 multisite study that 172 enrolled patients and 169 received at least 1 study dose, results demonstrated that bosutinib reduced the kidney growth rate in patients with ADPKD (66% slower with bosutinib, 200 mg/d, vs placebo annually).[76] There was no significant change in kidney function, as measured by eGFR, in the bosutinib and placebo groups during the 50-month treatment period.[76] No new toxicities aside from the gastrointestinal and liver-related adverse events, which were consistent with prior studies of bosutinib.[76]

Therapeutic MicroRNAs in ADPKD. MicroRNAs (miRNAs) are small noncoding RNAs that function as sequence-specific inhibitors of gene expression.[77] Dysregulated miRNAs have been identified in murine models of ADPKD.[77-81] miRNAs have emerged as potential new regulators of disease progression in PKD, specifically 2 miRNAs: miR-17∼92 cluster and miR-21.[77] The c-Myc oncogene transactivates miR-17∼92 cluster, which affects cyst epithelial metabolism to enhance cyst proliferation,[79] while the cAMP/cAMP response element-binding protein (CREB) pathway activates miR-21, which promotes cyst cell survival by inhibiting proapoptotic genes.[78,82,100] Thus, the miR-17 family is a promising drug target for ADPKD, and miR-17–mediated inhibition of

mitochondrial metabolism represents a potential new mechanism for ADPKD progression.[78]

Metformin. Metformin is a biguanide drug preferred as the first-line medication for the treatment of type 2 diabetes mellitus.[101] Based on experimental studies and 17 clinical observational studies, metformin seems to be a promising drug in the treatment of progressive kidney damage and could reduce all-cause mortality in patients with CKD.[102] Previous studies revealed that metformin can possibly reduce cyst formation and fluid secretion through its abilities to activate 5' AMP-activated protein kinase and suppress cystic fibrosis transmembrane conductance regulator and mTOR.[102,103] However, metformin could cause lactic acidosis in patients with advanced kidney failure with eGFRs < 30 mL/min.[103] Therefore, more studies are needed to assess the ability of metformin to improve clinical outcomes in patients with ADPKD.

Glucosylceramide Synthase Inhibitors. Sphingolipids and glycosphingolipids regulate many cellular processes, including modulation of cell signaling pathways.[103,104] Alterations of glycosphingolipid metabolism and elevated glucosylceramide (GlcCer) abundance have been documented in ADPKD in humans and the congenital polycystic kidney (CPK) mouse model.[103] The efficacy of GlcCer synthase inhibitor was tested in a *Pkd1* knockout mouse model of ADPKD and revealed low kidney GlcCer and GM3 abundance and effective inhibition of cystogenesis and fibrogenesis.[103] Therefore, more clinical trials are needed to study this approach for the treatment of PKD.

Glycogen Synthase Kinase-3β Inhibitors. The glycogen synthase kinase-3 (GSK3) is a family of serine/threonine protein kinases consisting of GSK3α and GSK3β isoforms derived from genes located on different chromosomes.[105] GSK3 regulates tubular injury and repair, inflammation, fibrosis, and urine concentration in the kidney.[105,106] They are targets for drug development in cancer, Alzheimer disease, and diabetes.[106,107] In the kidney, GSK3α and GSK3β positively regulate cAMP generation in response to vasopressin and are hence important for urine concentration. In PKD, loss of PC1 could increase GSK3β activity, which corresponds with the increase in cAMP levels in PKD and plays an important role in the proliferation of cyst-lining epithelial cells.[108] In recent studies of ADPKD mice models, pharmacologic inhibition of GSK3 reduced cyst volume and slowed the progression of PKD.[109,110] The results may be therapeutically useful to reduce cyst expansion and preserve kidney function in PKD.

VEGF Receptor 3 Ligand. VEGF, also known as VEGF-A, was initially described as an endothelial cell–specific growth factor that promotes vasculogenesis and angiogenesis and increases vascular permeability.[111] VEGF receptors (VEGFRs) are also expressed on a variety of nonendothelial cells, including renal tubular epithelial cells and podocytes.[112]

The major ligand for VEGFR3 is VEGF-C, which enhances growth, survival, and migration of adult lymphatic endothelia.[113] They are also required for podocytes that require VEGF signaling for survival through VEGF2R or paracrine signaling mechanisms.[112,114]

Treatment with VEGF-C enhanced VEGFR3 phosphorylation in the kidney, normalized the pattern of the pericystic network of vessels, and was associated with significant reductions in cystic disease, serum urea nitrogen, and serum creatinine levels.[115] Overall, studies highlight VEGF-C as a potential new target for some aspects of PKD, including hepatic cysts.[116] It is also possible that other diseases associated with microvascular abnormalities are possibly driven by the defective expression and activity of the VEGF pathway.

It is worth mentioning that octreotide, an analogue of somatostatin that inhibits cAMP accumulation, has been shown to reduce the progression of liver and kidney cysts in a PKD rat model.[107] This drug failed to show beneficial effects compared with a placebo in a recent 3-year randomized controlled trial in patients with ADPKD.[117] More studies are needed to determine its benefits.

CONCLUSIONS

New theoretical and clinical breakthroughs are elucidating the pathophysiology, natural course, and clinical approach to ADPKD.[13,56] The immediately available intervention that will likely result in prolongation of dialysis-free time in select patients is tolvaptan therapy. The REPRISE trial provides an expectation that at CKD stage 3, an expected increase in dialysis-free renal survival of about 1.5 years up to 7.3 years depending on the baseline eGFR and the initiation time of the treatment can be obtained in rapidly progressive ADPKD with the use of tolvaptan.[57] The risks notwithstanding, it represents a new hope in the battle against premature kidney failure in ADPKD.[118,119]

ARTICLE INFORMATION

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