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Novel therapeutic approaches to Autosomal Dominant Polycystic Kidney Disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder characterized by the progressive growth of renal cysts that, over time, destroy the architecture of the renal parenchyma and typically lead to kidney failure by the 6th decade of life. ADPKD is common and represents a leading cause of renal failure worldwide. Currently, there are no FDA approved treatment for the disease, and the existing standard of care is primarily supportive in nature. However, significant advances in the understanding of the molecular biology of the disease have inspired investigation into potential new therapies. Several drugs designed to slow or arrest the progression of ADPKD have shown promise in pre-clinical models and clinical trials, including vasopressin receptor antagonists and somatostatin analogs. This article examines literature underlying the rationale for molecular therapies for ADPKD and reviews the existing clinical evidence for their indication for human patients with the disease.

Keywords

Autosomal Dominant Polycystic Kidney Disease (ADPKD); Polycystin-1 (PC1); Polycystin-2 (PC2); Cyclic adenosine 3'-5' monophosphate (cAMP); End stage renal disease (ESRD); Vasopressin V2 receptor (V2R) antagonists; Somatostatin analogues; AMP-activated protein kinase (AMPK) activators; Cystic fibrosis transmembrane conductance regulator (CFTR) inhibitors; mammalian target of rapamycin (mTOR) inhibitors; Src inhibitors

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the fourth leading cause of renal failure in adults and affects approximately 1:500 to 1:1000 live births¹. Individuals

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with the disease are born with normal renal function that declines progressively as renal cysts grow and expand, eventually leading to end stage renal disease (ESRD) in many patients by the 6th decade of life. ADPKD is a multisystem disease characterized by the progressive development of bilateral renal cysts, and can additionally present with a wide variety of extrarenal manifestations that include hepatocystic disease, intracranial aneurysms and cardiac defects among others². Currently there exists no FDA-approved therapy for the disease outside of supportive care, including renal replacement therapy for those who develop ESRD.

ADPKD is caused by mutations in the genes *PKD1* or *PKD2*, which encode the proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Whether a third gene may explain a small number of unlinked families is still unknown. While the exact mechanisms of pathogenesis remain to be elucidated, the dysregulation of intracellular Ca⁺⁺ signaling observed to follow the loss of functional PC1 and PC2 is thought to induce important changes in cyclic nucleotide metabolism that drive the hypersecretory and hyperproliferative cellular phenotype characteristic of ADPKD^{3,4,5}.

In the last decade, advances in the understanding of the molecular biology of ADPKD have prompted the study of a number of pharmacological therapies designed to slow or arrest the progression of the disease. Most therapies recently or currently being tested are aimed at 1) reducing cyclic adenosine 3'-5' monophosphate (cAMP) levels, 2) inhibiting tubular cell proliferation and 3) reducing fluid secretion by cystic epithelium. This article focuses on new therapies that have recently completed or are currently being tested in clinical trials of ADPKD

CLINICAL COURSE, CRISP and HALT TRIALS in PATIENTS WITH ADPKD

A significant barrier to the development of an effective therapy for ADPKD has been the lack of a sensitive means by which to measure the progression of the disease over time. Serum creatinine is not typically elevated in patients until late in the course of disease progression, by which time significant and irreversible damage to the renal parenchyma has already occurred. New markers of disease progression were needed to provide better prognosis and assess the efficacy of candidate therapies in clinical trials for patients with ADPKD. For this reason, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) was founded to investigate the use of magnetic resonance imaging (MRI) to quantify renal expansion as a means of non-invasive surveillance of patients with ADPKD. CRISP has produced valuable information, identifying baseline predictors of disease severity and renal function decline.

CRISP I enrolled 241 patients with ADPKD between the ages of 15 to 45 with a minimum creatinine clearance of 70 mL per minute, of whom sixty percent were also comorbid with hypertension. Patients were assessed annually from 2001 to 2005, to investigate the correlation between total kidney volume (TKV) and glomerular filtration rate (GFR), as measured by MRI and iothalamate clearance, respectively. Two years after the completion of CRISP I, 201 participants re-enrolled into an additional 5-year follow-up study (CRISP II). Participants had TKV and GFR measurements as in CRISP I, but this time were

evaluated every two years. The main findings from the initial study (241 participants) were that TKV increased steadily in all over time, but at a uniform rate unique to each patient. The mean baseline TKV was 1076 mL with a mean increase of 63.4 mL (5.27%) per year, a rate significantly correlated with the measured decline of GFR. However, the rate of TKV increase and the corresponding rate of decline in GFR varied widely among patients. When grouped by baseline TKV, only patients with an initial value greater than 1500 mL showed a significant average decrease in GFR slopes (-4.3 mL/min/year)⁶. Despite heterogeneity, the strong correlation between baseline TKV and the rate of decline in GFR, provided evidence that TKV might effectively forecast the age of progression to ESRD. From the 201 re-enrollees (CRISP II), 194 completed an average 8 years of follow-up. The primary endpoint from this phase of the study was renal insufficiency, defined as stage 3 CKD or a GFR <60 mL/min per 1.73 m². The overall annual rate of increase in TKV was similar to the initial period of follow-up ($5.5\% \pm 3.8\%/yr$ versus $5.3\% \pm 4.0\%/yr$). In addition, this extension in follow-up period confirmed the exponential relationship between TKV and age observed after 3 years. By receiver operator characteristic (ROC), an htTKV value of 600mL/m or greater forecasted the onset of renal insufficiency within 8 years. Further analysis showed that each 100mL increment of baseline htTKV increased the odds of developing renal insufficiency within 8 years by nearly 150 percent⁷. This confirmed the findings of CRISP I and implied that just a single determination of htTKV may be sufficient for prognosis.

Cardiovascular disease, particularly hypertension and its sequelae, is a leading cause of morbidity and mortality in patients with ADPKD⁸. However, to date, an optimal antihypertensive therapy for ADPKD has yet to be defined. The HALT-PKD is an ongoing clinical trial designed to evaluate whether there is a difference in the progression, or in slowing down the decline of renal function between those given dual angiotensin converting enzyme (ACEi) inhibitor and angiotensin-II receptor blocker (ARB) therapy versus an ACEi alone, in patients with GFR > 60 mL/min per 1.73 m² (study A), and in patients with GFR 25 to 60 mL/min per 1.73 m² (study B) respectively. In those with GFR > 60 mL/min per 1.73 m², the study will further investigate the effect of medicating to a standard (120-130/70-80 mmHg) versus low (95-110/60-75 mmHg) target blood pressure on renal function over time⁹. Initial analysis of baseline parameters have shown that estimated GFR and higher urine albumin were independently associated with a higher baseline htTKV, confirming the findings of the CRISP consortium¹⁰.

Together, CRISP and HALT-PKD trials have provided important insight into the progression of ADPKD that will prove beneficial for both patient management and the evaluation of candidate therapeutics in clinical trials

GENETICS & PATHOPHYSIOLOGY

The majority of the patients with ADPKD present mutations in the *PKD1* gene; approximately 85%, which is associated with a more severe renal cystic disease than mutations in *PKD2*¹¹. On average, patients with mutations in *PKD1* develop ESRD at younger ages compared to patients with *PKD2* mutations (54.3 vs 74 years of age), but extrarenal phenotypes are known to affect patients with mutations on both genes¹². Extensive genetic analysis of patients with ADPKD has revealed that a wide variety of

mutations can cause the disease. To date, 1272 and 202 confirmed pathogenic mutations have been described in *PKD1* and *PKD2*, respectively. <http://pkdb.mayo.edu/index.html>

It has been held that the position of the mutation in *PKD1* or *PKD2* plays a role in determining the severity of disease^{13, 14}, but recent clinical evidence suggests that the type of mutation may be more important, as patients with truncating mutations have been shown to present with more severe kidney disease than those with non-truncating mutations^{15, 16}. Hypomorphic mutations and incompletely penetrant *PKD1* or *PKD2* alleles have been described. A hypomorphic allele alone may result in mild cystic disease while two such alleles can cause typical to severe disease, and one hypomorphic allele in combination with an inactivating allele is associated with early onset severe disease.

The pathophysiology of ADPKD originates from the loss of functional polycystin-1 (PC1) and polycystin-2 (PC2), the protein products of *PKD1* and *PKD2* respectively. These proteins are known to form a complex that is believed to function as a transient receptor potential (TRP) channel involved in the regulation of intracellular calcium homeostasis^{17, 18}. Research indicates this complex to be localized to the primary cilium¹⁹ as well as the endoplasmic reticulum (ER)²⁰, where it exerts specific influence on calcium concentrations in several subcellular compartments^{21, 22}. In the primary cilium, it is believed that the PC1-PC2 complex functions as a mechanoreceptor to induce the influx of extracellular calcium in response to fluid shear stress²³⁻²⁵, while in the ER it associates with the ryanodine receptor (RyR) and functions as a calcium release channel (Figure 1)^{20, 26}. Recent evidence suggests that ciliary calcium signaling is isolated from the cytoplasm, and that any influence it may exert on the rest of the cell is not due to bulk entry of calcium via the primary cilium^{27, 28}.

While the mechanisms are poorly understood, loss of the functional PC1-PC2 complex results in phenotypic changes which include the inability to maintain planar cell polarity, an increase in proliferation and apoptosis, the expression of a secretory phenotype, and remodeling of the extracellular matrix. The major signaling pathways implicated in these phenotypic changes include the intracellular deregulation of calcium homeostasis, cAMP accumulation and activation of protein kinase A (PKA), activation of mitogen activated protein (MAPK) and mammalian target of rapamycin (mTOR) kinases, canonical Wnt signaling and other intracellular signaling mechanisms.^{5, 29, 30}

ROLE of cAMP in PKD

Many animal models of PKD have increased levels of intracellular cAMP not only in the kidney but also in other tissues affected by the disease, including cholangiocytes³¹, vascular smooth muscle³² and choroid plexus³³, which has been shown to be of central importance to the pathogenesis of ADPKD.

Cyclic AMP levels are normally regulated by the balanced activity of soluble and G-protein coupled receptor (GPCR) associated adenylyl cyclases (ACs) and phosphodiesterases (PDEs). Increased levels of cAMP have been attributed to a variety of mechanisms, most of which are related to altered calcium signaling. Reduced calcium is known to inhibit directly or indirectly the activity of PDE1 and PDE3 respectively, and to activate membrane-bound AC6, thus producing a net increase in cAMP concentration (Figure 2). Likewise, depletion

of calcium in the ER (perhaps due to leakage of PC2²²) induces the assembly of stromal interaction molecule 1 (STIM1) and the concomitant activation of AC6³⁴. The compartmentalized nature of cAMP signaling³⁵ suggests that certain ACs and PDEs may be more important than others to the pathogenesis of ADPKD due to their influence on specific subcellular pools of cAMP. The specific importance of AC6 was underlined in a recent study in which the collecting duct specific ablation of *Pkd1* induced a renal cystic phenotype that was rescued by the concomitant knockout of AC6³⁶. Similarly, recent studies suggest that specific PDEs, including PDEs 1, 3, and 4, may be more important than others in the pathogenesis of ADPKD^{37, 38}. The compartmentalization of cAMP regulatory enzymes may present a unique future opportunity for specifically targeted therapies.

cAMP exerts its effects via PKA, an intermediate identified as contributing to several distinct elements of ADPKD pathophysiology. It is possible that PKA signaling may induce dysfunctional renal development via the aberrant activation of Wnt/ β -catenin signaling^{39, 40}, a pathway known to be disrupted in ADPKD⁴¹. This sustained PKA-dependent activation of canonical Wnt signaling interferes with nephrogenesis and results in disorganized epithelial clusters and dilated renal tubules⁴². Furthermore, cAMP signaling has been demonstrated to be involved with the hypersecretory cellular behavior that drives cyst expansion. Forskolin, a drug that upregulates cAMP synthesis, was shown early on to induce fluid secretion in intact cysts excised from patients with ADPKD⁴³. The bulk of this fluid secretion is driven by the active transport of chloride into the lumen of the cyst^{44, 45}, which is drawn across the basolateral membrane epithelium by the combined activity of the Na⁺K⁺ATPase and the Na⁺K⁺Cl⁻ cotransporter. PKA-mediated phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR) induces the opening of its channel and permits chloride ions to flow down the electrochemical gradient and into the cyst⁴⁶. This is supported by the observation that pathogenic mutations of the CFTR in the context of PKD function to attenuate cystogenesis both in laboratory studies⁴⁷ and in patients with ADPKD.^{48, 49}

PKA-mediated cAMP signaling is also believed to be responsible for much of the hyperproliferative cellular phenotype observed in ADPKD. Treatment with cAMP induces proliferation in primary cells derived from polycystic renal tissue in an extracellular signal-regulated kinase (ERK) dependent manner, but inhibits proliferation in cells derived from healthy human kidneys^{50, 51}. PKA-mediated ERK signaling has been shown to activate mTOR^{52, 53}, a protein that forms two distinct multimeric complexes (mTORC1 and mTORC2) that regulate a variety of cellular processes involved with growth, proliferation, and autophagy⁵⁴. The upregulation of a number of other pro-proliferative transcription factors have been linked to PKA-mediated cAMP signaling in PKD, including cAMP response element-binding protein (CREB)⁵⁵, paired box gene 2 (Pax2)⁵⁶, and signal transducer and activator of transcription 3 (STAT3)^{5, 57}. STAT3 is of particular interest due to its role in the development and maintenance of a pro-inflammatory cellular environment, a characteristic of cystic tissue in PKD⁵⁸. STAT3 activation is known to induce the secretion of a number of pro-inflammatory soluble factors which, in turn, activate tumor-associated macrophages in an alternative pathway (M2) dependent manner⁵⁹. Research indicates that macrophages undergo alternative activation in response to unidentified elements secreted by

the tubular epithelium of PKD model animals. Alternatively activated macrophages have been shown to induce cellular proliferation and fibrogenesis in the tissues of orthologous models for PKD, and depletion of these macrophages via intraperitoneal clodronate injections has been shown to attenuate the severity of PKD *in vivo*^{60, 61}.

THERAPIES TARGETING cAMP SIGNALING

The importance of cyclic nucleotide signaling in ADPKD, specifically cAMP, provides rationale for therapies towards decreasing its levels (i.e. vasopressin V2 receptor antagonists, somatostatin analogs) and have been used in clinical trial with promising results.

Vasopressin V2 receptor (V2R) antagonists

Vasopressin is a small peptide hormone secreted by the pituitary gland in response to increased plasma osmolality, and functions to induce the reabsorption of water in the collecting duct by binding to the G-protein coupled arginine vasopressin (AVP) V2 receptor. In doing so, AVP also stimulates the production of cAMP via membrane bound adenylate cyclase 6. Circulating AVP levels and renal V2R expression are increased in rodent PKD, possibly due to AVP resistance manifested by a urinary concentrating defect. As the expression of the V2 receptor is almost exclusive to the late nephron; the site of renal cystogenesis in ADPKD,⁶² V2R are an attractive target to modulate cAMP with minimal side effects.. Several preclinical trials have shown that treatment with AVP V2 receptor antagonists successfully slow disease progression in orthologous animal models of both ARPKD and ADPKD, including those with mutations on *Pkd2*^{63, 64}. The importance of circulating AVP in the natural progression of the disease was demonstrated by the finding that increased water intake reduced the progression of renal cystic disease in an ARPKD model (PCK rat)⁶⁵. This was confirmed when the same animals were bred with rats lacking circulating AVP (*AVP*^{-/-}, so-called Brattleboro rats⁶⁶), producing double-homozygous offspring (*AVP*^{-/-} *Pkhd1*^{-/-}) that were shown to have almost normal renal structure and function, but could be induced to develop renal cystic disease through the administration of synthetic 1-deamino-8-D-arginine vasopressin (DDAVP), a synthetic V2 receptor agonist⁶⁷.

Tolvaptan is a highly potent and selective AVP V2 receptor antagonist and has been shown to slow the progression of PKD in preclinical trials⁶⁸ In the US, it is currently approved for the treatment of hypervolemic and euvolemic hyponatremia. In Japan, it has now been approved as a therapy to slow down the progression of ADPKD in patients with rapidly growing kidneys. Open-label Phase 2 clinical trials in the US⁶⁹ and Japan⁷⁰ have demonstrated the long-term safety and tolerability of tolvaptan and generated pilot efficacy data..

The Tolvaptan Efficacy and Safety in Management of ADPKD and its Outcomes (TEMPO) 3:4 trial was a phase 3, multicenter, randomized, double blinded, placebo controlled, parallel-group clinical study, designed to assess the impact of tolvaptan therapy on the progression of ADPKD⁷¹. One thousand, four hundred and forty five ADPKD patients aged 18-50 years, with a TKV >750 mL and CrCL>60 mL/min, across 129 sites worldwide were enrolled in the study between January 2007 and January 2009. Of these, 961 initiated

treatment with tolvaptan and the other 483 (one withdrawal pre-treatment) with placebo. One thousand, one hundred and fifty seven patients completed all three years of the trial, corresponding to 77% and 86.2% of the tolvaptan and placebo group, respectively. All patients with at least one follow-up MRI, 1307 of the original 1445 patients, were included in the primary efficacy analysis and all 1445 in the secondary safety analysis. In the tolvaptan group, therapy consisted of either a high dose (120mg/day, n=404), medium dose (90mg/day, n=157), or low dose (60mg/day, n=179), with high rates of self-reported adherence in the majority of patients. The primary end point for the study was the annual rate of percent change in TKV as measured by MRI, with several secondary endpoints corresponding to a measurable decline renal function, including a composite endpoint of investigator-assessed disease progression.

The results showed that during the 3-year trial tolvaptan reduced the rate of kidney growth by nearly 49%. Total kidney volume increased an average of 2.8% per year in patients treated with tolvaptan versus 5.5% per year growth rate in the placebo group ($p<0.001$). This corresponded to the observed difference in eGFR slope (as measured by the reciprocal of serum creatinine level) between the two groups: -2.61 mg/mL per year versus -3.81 mg/mL per year, for tolvaptan and placebo respectively ($p<0.001$), and the average increase in serum creatinine from 1.05 to 1.21 mg/dL versus 1.04 to 1.27 mg/dL in the tolvaptan and placebo respectively ($p<0.001$). Furthermore, analysis of the key secondary composite endpoint of time to clinical progression showed fewer ADPKD-related events per 100 person-years of follow-up with tolvaptan than placebo (hazard ratio 0.87, 95% C. 0.78 to 0.97, $P=0.01$). The protective effect was observed across all prespecified subgroups, including stratification by sex, age, diagnosis of hypertension, baseline TKV and baseline creatinine clearance. However, this effect was nominally greater in patients 35 years of age or older and those with hypertension and/or a TKV of greater or equal to 1500mL. It was also observed that the effect of tolvaptan on renal volume expansion was larger in the first year than in the second and third years. The frequency of adverse events (AEs) experienced by tolvaptan and placebo group were roughly equivalent; 97.9% vs 97.1% respectively. Increased aquaresis related AEs (thirst, polyuria, nocturia and polydipsia) were higher in frequency in the tolvaptan group and ADPKD-related AEs (kidney pain, hematuria, urinary tract infection, and back pain) were higher in the placebo group. Serious AEs occurred in at least 0.5% of the patients in either group. The most frequent SAEs occurring in the tolvaptan treatment group were: alanine aminotransferase elevation 0.9%, aspartate aminotransferase elevation 0.9%, chest pain 0.8% and headache 0.5%. In the placebo group, most frequent SAEs included: pyelonephritis 1.0%, renal-cyst infection 0.8%, renal-cyst hemorrhage 0.8%, renal pain 0.8%, appendicitis 0.8%, nephrolithiasis 0.6%, urinary tract infection 0.6%, and hypertension 0.6%.

Currently, tolvaptan is not approved for the treatment of ADPKD in the United States.

Somatostatin Analogs

Somatostatin (SST) is a peptide hormone involved in the endocrine regulation of cellular metabolism. Interaction with the G-protein coupled somatostatin receptors (SSTRs 1-5) inhibits adenylate cyclase mediated cAMP synthesis, which functions to inhibit proliferation

and secretion in a variety of tissues. Treatment with somatostatin has been shown to inhibit collecting duct specific cAMP synthesis *in vitro*⁷² and *in vivo*⁷³, and has been shown to have similar effects in cholangiocytes as well^{74, 75}. While the anti-proliferative and secretory effects of somatostatin have long been of interest to medical science, the three-minute serum half-life of somatostatin makes it impractical for therapeutic use. For this reason, the synthetic analogs octreotide, lanreotide and pasireotide were developed as stable alternatives. These analogs differ in stability and receptor selectivity; octreotide and lanreotide have a half-life of 2 hours in circulation and bind with high affinity to SSTRs 2&3 and moderate affinity to SSTR 5. Pasireotide, however, binds with high affinity to all SSTRs except SSTR4 and has a serum half- life of 12 hours⁷⁶. Preclinical studies demonstrated that octreotide and pasireotide could successfully reduce proliferation and intracellular cAMP concentrations in cholangiocytes, both *in vitro* and *in vivo*^{31, 77}, indicating that somatostatin analogs may be an effective therapy for ADPKD patients with cystic liver disease.

Three small, randomized, placebo-controlled clinical studies (NCT00309283, NCT00426153, NCT00565097) provided initial evaluation of octreotide or lanreotide treatment in ADPKD and polycystic liver disease (PLD). A 6 months cross-over study of octreotide treatment (40 mg i.m. once every 28 days) was well tolerated and reduced the rate of TKV growth by approximately 56% (71mL and 162mL for treatment and placebo respectively) in 14 patients with ADPKD (mean baseline GFR 57.1 mL/min, range 24.4 – 95.3 mL/min). GFR, measured as iothexol clearance, did not change significantly during both treatment periods.⁷⁸ In a secondary *post hoc* analysis, significant changes in liver volumes between the two treatment periods were found. Liver volumes significantly ($p < 0.05$) decreased by 71 ± 57 mL during octreotide versus 14 ± 85 mL increase while no treatment.⁷⁹

Another 6-month study compared treatment with Lanreotide (120 mg once every 28 days subcutaneously) to placebo in 54 patients with PLD, (of which 32 had ADPKD) Total liver volume decreased significantly ($p < 0.01$) by 2.9% (4606mL to 4471mL) in Lanreotide versus a 1.6% increase in the placebo group (4689mL to 4895mL). A *post hoc* stratification for ADPKD/PLD revealed similar changes in liver volume between both disease groups, concluding that the change in liver volume was independent of cause of disease and for both, the difference between placebo and lanreotide treatment was significantly different ($p < 0.01$).⁸⁰ A 6 month open label extension, where 41 patients (25 ADPKD) re-enrolled to complete a total 12 months of lanreotide treatment, showed median decrease in liver volume of 4% ($p < 0.05$) in the overall study population. The greatest effect was observed during the first 6 months of treatment and liver volume remained unchanged during the following 6 months. In 22 patients that had a CT scan 6 months after stopping 12 months of lanreotide treatment, a 4% rebound growth in liver volume was observed.⁸¹

Another octreotide study (40 mg i.m every 28 days) in 42 patients with PLD (of which 34 had ADPKD) showed a reduction in liver volume of 4.95% in the octreotide group compared with an increase of 0.92% in the placebo group. In addition, TKV remained practically unchanged in octreotide treated patients but increased significantly ($p = 0.045$) in non-treated patients ($+0.25\%$ vs 8.61%) over the course of a year⁸². This study was also

continued as open-label for an additional 12 months. In the initial octreotide treated group, the change in liver volume was maintained, but no significant change was observed during the following 12 months (-0.77% year 1 vs. year 2 $p=0.57$). Patients that crossed to octreotide experienced a significant 7.66% reduction in liver volume by the end of the octreotide treatment period (year 1 to year 2 $p=0.01$) compared to the initial 0.92% increase during placebo (Baseline to year 1).⁸³

Another study that included 44 patients (29 PCLD, 15 ADPKD) comparing the effects of octreotide alone (40 mg i.m. once every 28 days) vs octreotide plus everolimus (40 mg i.m. once every 28 days + everolimus 2.5 mg daily) (NCT01157858) found no significant decrease in liver volume among the two groups (3.5% vs 3.8% ; $p = 0.73$) over the course of 48 weeks.⁸⁴

Most recently, a three-year multicenter, randomized, single-blind, placebo-controlled, parallel-group study of octreotide treatment in Italy published results supporting the use of octreotide in ADPKD⁸⁵. Seventy-nine adult (>18 years old) patients with an eGFR greater than $40\text{mL}/\text{min}/1.73\text{m}^2$ were enrolled in either a treatment (two 20mg i.m. octreotide-LAR injections every 28 days) or placebo group. Of these, 37 octreotide-LAR and 36 placebo treated patients completed the 3 year study. After year one of follow up, it was found that octreotide reduced the average increase in TKV by nearly two-thirds that of the control group (46.2mL vs. 143.7mL , respectively $p=0.032$). However, at three year follow-up, even though TKV increase in the octreotide-LAR group was smaller compared to placebo group, the difference in TKV growth was not significant between the two groups ($p=0.25$).

Several larger clinical trials of somatostatin analogs for ADPKD and PLD are currently underway. A European study designed to examine the renoprotective efficacy of lanreotide in ADPKD, DIPAK, is ongoing. This multicenter clinical trial will enroll 300 ADPKD patients with an eGFR between 30 and $60\text{mL}/\text{min}/1.73\text{m}^2$ and measure the effect of lanreotide treatment (120mg q.28 days via subcutaneous injection) over the course of two and a half years⁸⁶. The primary study outcome is the slope of eGFR measurements taken between weeks 12 and 120, with secondary outcome parameters of changes in kidney volume, liver volume, and self-reported quality of life.

THERAPIES TARGETING mTOR SIGNALING

It had been observed that contiguous germline deletions affecting *PKD1* and the immediately adjacent *TSC2*, a gene associated with tuberous sclerosis, led to abnormally severe disease in patients⁸⁷⁻⁸⁹. This gave rise to the hypothesis that the two genes may function as part of a common pathway. PC1 physically interacts and retains tuberlin at the plasma membrane thus preventing it phosphorylation by AKT (protein kinase B) and its ability to inhibit the mTOR pathway⁹⁰. Other studies have shown that ERK activation, downstream from PKA activation, leads to phosphorylation of tuberlin preventing its association with hamartin and the inhibition of Rheb and mTOR by the tuberlin-hamartin complex.^{52, 53}

Early preclinical studies in rodent models of PKD demonstrated that mTOR was highly upregulated in the cystic epithelium^{91, 92} and that sirolimus^{93, 94} treatment decreased

proliferation in cystic and non-cystic tubules, markedly inhibited renal enlargement and cystogenesis and prevented the loss of kidney function giving rise to the hope they would be effective in humans as well. Further differences between rat and mouse studies raised questions on whether doses of mTOR inhibitors necessary for effectiveness in PKD were feasible in the clinical setting. At doses and blood levels achievable in humans, sirolimus and everolimus were effective in a rat model of PKD affecting the proximal tubules but not in an orthologous model affecting the distal nephron and collecting duct.⁹⁵ Lower dose treatment in an orthologous mouse model similarly demonstrated no effect⁹⁶.

Clinical trials for mTOR inhibitors in patients with ADPKD have been largely disappointing, possibly because blood levels capable to inhibit mTOR activity in peripheral blood mononuclear cells are not sufficient to inhibit mTOR activity in the kidney.⁹⁷ The use of sirolimus in the treatment of patients with ADPKD showed only a small benefit (SIRENA)⁹⁸, (RAPYD)⁹⁹ or no benefit (SUISSE)¹⁰⁰ on kidney volume or GFR. Additionally, one clinical trial using everolimus showed inhibition of kidney growth but more decline in eGFR.¹⁰¹

Results from a new pilot trial of rapamycin in 30 adult patients with ADPKD¹⁰² have been recently published. Patients were randomly assigned to low-dose (n=10, 2–5 ng/ml rapamycin), standard-dose (n=10, 5–8 ng/ml rapamycin) or standard care (n=10). Braun et al. hypothesized that a more accurate measure of change in GFR using ¹²⁵I-iothalamate (iGFR) as compared by eGFR (CKD-EPI) (primary endpoint) would reveal a treatment effect with better tolerated low-dose rapamycin treatment for 12 months. The results show that low dose rapamycin was associated with improved short-term (6 and 12 months) renal function as measured by change in iGFR without significant change in TKV or eGFR.

Other therapeutic targets currently in clinical trials for ADPKD

Botusimib—The Src inhibitor SKI-606 retarded cyst growth in PCK rats and bpk and *Pkd1* heterozygous mice.^{103, 104} A phase II, multicenter, randomized, double blind, placebo control clinical trial with bosutinib (a Src/Abl inhibitor) is currently ongoing (NCT01233869).

Statins—A randomized double-blind placebo-controlled phase III clinical trial (from 2007 to 2012) to assess the effect of pravastatin on HtTKV and left ventricular mass index (LVMI) by MRI and urine microalbumin excretion (UAE) in children and young adults with ADPKD was recently completed and results are now available. The trial enrolled 110 patients (8–22 years of age) of whom 91 completed the trial. Those patients randomized to pravastatin (n=56) demonstrated significantly less increase in HtTKV over 3 years compared to patient randomized to placebo (n=54, 23%±3% for statin versus 31%±3% for placebo per 3 years; *P*=0.02). There was no significant change in creatinine clearance, urine protein excretion or LDL cholesterol between groups. Pravastatin was well tolerated with no apparent adversity. The findings support a role for early intervention with pravastatin in ADPKD.¹⁰⁵

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SUMMARY

ADPKD is a disease of remarkably complex genetic and molecular etiology. Advances in the understanding of its pathogenesis, in particular the role of cAMP, have led to the development of candidate therapies that have demonstrated significant promise in clinical trials. Unlike the existing standard of care, these treatments are designed to attenuate the progression of the disease in target tissues and to prevent the onset of organ failure. Unfortunately, the limitations of clinical study design hamper accurate evaluation of their efficacy in patients. Traditional surrogate markers of renal function are poorly correlated to the progression of ADPKD, making it difficult to assess the impact of a given therapy over the short timespan of a clinical trial; Total kidney volume may provide a more accurate alternative. Vasopressin V2 receptor antagonists and somatostatin analogs have been shown to safely slow kidney growth and protect renal function in patients with ADPKD, and represent the most well-characterized and promising candidate therapies to date. While the search for a cure is far from over, it seems increasingly possible that ADPKD will one day be a treatable disease. For this to occur, advances at the laboratory benchtop must continue for us to provide relief at the patient bedside.

Figure 1. Schematic representation of the *PKD1* protein, polycystin-1 (PC1) and the *PKD2* protein, polycystin-2 (PC2), and their interaction in a normal tubular cell

PC1 and PC2 are found on the primary cilium but also in the plasma membrane (PC1) and the endoplasmic reticulum (ER) (PC2). The PC1/PC2 complex in primary cilia senses flow and translates it into Ca^{2+} entry and ER Ca^{2+} release. Disruption of PC1/PC2 in ADPKD lowers intracellular Ca^{2+} and results in up regulation of cAMP signaling and increased fluid secretion and cell proliferation.

FIG 2.
PKD SIGNALING DIAGRAM w/ TARGETS OF INTERVENTION