Therapeutic Advances in the Treatment of Polycystic Kidney Disease

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End-stage renal disease · Polycystic kidney disease · Total kidney volume

Abstract
The spectrum of polycystic kidney disease (PKD) comprises a family of inherited syndromes defined by renal cyst formation and growth, progressive renal function loss and variable extrarenal manifestations. The most common form, autosomal-dominant PKD is caused by mutations in one of two genes, PKD1 or PKD2. Recent developments in genomic and proteomic medicine have resulted in the discovery of novel genes implicated in the wide variety of less frequent, recessive PKD syndromes. Cysts are the disease, and overall cystic burden, measured by MRI as total kidney volume, is being established as the best available biomarker of disease progression. Current state-of-the-art therapy is aimed at quality treatment for chronic renal insufficiency and cyst-related complications. Recent therapeutic studies have focused on mechanisms reducing intracellular cyclic AMP levels, blocking the renin-angiotensin-aldosterone system and inhibiting the mTOR-signaling pathway. PKD therapies with vaso-pressin antagonists and somatostatin analogues result in the reduction of intracellular cAMP levels and have shown limited clinical success, but side effects are prominent. Similarly, mTOR pathway inhibition has not shown significant therapeutic benefits. While the HALT-PKD study will answer questions by the end of 2014 about the utility of renin-angiotensin-aldosterone system blockade and aggressive blood pressure control, the next generation of PKD therapy studies targeting proliferative mechanisms of cyst expansion are already under way. Advances in research on the molecular mechanisms of cystogenesis will help design novel targeted PKD therapies in the future.

Introduction
Cystic kidney diseases comprise a spectrum of genetic disorders characterized by renal cyst formation and growth, along with variable extrarenal manifestations. The most common syndrome is represented by polycystic kidney disease (ADPKD), with an incidence ranging from 1:400 to 1:1,000 births and accounting for about 4.4% of end-stage renal disease (ESRD) cases in the USA [1]. Progression of cyst growth and chronic kidney disease is inevitable, leading to ESRD and the need for renal replacement therapy. Advances in genomics and proteomics have led to the identification of many disease genes that are mutated in less common forms of cystic kidney disease, contributing to our current understanding of polycystic kidney disease (PKD) pathogenesis. Morbidity and mortality of PKD are related to the progressive nature of chronic renal insufficiency, the burden of cyst-related complications (pain, stones, infection, hemorrhage) and the presence of polycystic liver...
disease, intracranial aneurysms and other extrarenal manifestations (Table 1). As a dominant genetic trait, ADPKD often affects multigenerational family members, but the course of the disease can vary widely within a single family. Cysts are the disease, and treatment strategies are being developed to specifically prevent or delay cyst formation and expansion at an early stage; however, no such therapy is currently approved. In this minireview, we will emphasize a number of key pathogenic principles, the recent advances in the treatment of PKD and future perspectives.

**Molecular Basis of Disease**

ADPKD is a monogenic disease caused by mutations in one of two genes, PKD1 or PKD2. PKD1 gene mutations account for about 75% of all cases, giving rise to ADPKD type I, while PKD2 mutations account for the remaining 25% (ADPKD type II). Recent studies have suggested that the prevalence of PKD2 mutations may be higher, between 26 and 36% [2]. The PKD1 gene product, polycystin-1, is a large 460-kDa transmembrane glycoprotein of largely unknown biochemical function [3]. It has been shown to interact with the PKD2 gene product, polycystin-2, through its C-terminal intracellular tail. Polycystin-2 is characterized as a nonselective cation channel, and believed to regulate intracellular calcium homeostasis [4]. Subcellular localization of both proteins to primary cilia is of paramount importance. Almost all other gene products implicated in the spectrum of PKD syndromes localize to and exert their biochemical function in primary cilia [5]. Although physiologic PKD protein function was believed to involve intracellular signaling through a polycystin-2-mediated ciliary calcium influx, recent studies have revealed that knockdown of polycystin-2 did not alter ciliary calcium levels. Instead, novel evidence from electrophysiological measurements have emphasized the importance of the gene products PKD1L1 and PKD2L1 (PKD1-like-1 and PKD2-like-1, respectively), which form a heteromeric ion channel [6]. How PKD1L1/PKD2L1-related mechanisms connect to the cellular functions of PKD1 and PKD2 gene products in renal tubular epithelia will need to be elucidated, but it is likely that the model of PKD1/2-generated ciliary calcium transients leading to altered cytoplasmic calcium homeostasis will see future updates. Cells lacking polycystin-1 or polycystin-2 have decreased levels of intracellular calcium, consecutively activating adenylyl cyclase and resulting in higher cAMP levels [7]. These events are

**Table 1. Other extrarenal manifestations of ADPKD**

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Associated</th>
<th>Percent affected</th>
<th>Screen</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac valve abnormalities</td>
<td>yes</td>
<td>mitral valve prolapse 25%</td>
<td>no</td>
<td>screen only if cardiovascular signs/symptoms</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>yes</td>
<td>up to 35%</td>
<td>no</td>
<td>screen only if cardiovascular signs/symptoms</td>
</tr>
<tr>
<td>Extracranial aneurysms</td>
<td>yes, case reports</td>
<td>unknown</td>
<td>no</td>
<td>clinicians should be aware of vascular phenotype in some patients</td>
</tr>
<tr>
<td>Arachnoid cysts</td>
<td>yes</td>
<td>8–12%</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Spinal meningeal cysts</td>
<td>yes</td>
<td>1.7%</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cysts</td>
<td>yes</td>
<td>10%</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>possibly in association with ESRD</td>
<td>20–25% in ESRD</td>
<td>no</td>
<td>increase incidence in patients who have reached ESRD</td>
</tr>
<tr>
<td>Abdominal hernias</td>
<td>yes</td>
<td>unknown</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Seminal vesicle cysts</td>
<td>yes</td>
<td>~40%</td>
<td>no</td>
<td>does not correlate with abnormal semen parameters</td>
</tr>
<tr>
<td>Male infertility</td>
<td>unknown</td>
<td>unknown</td>
<td>no</td>
<td>abnormal semen parameters reported</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>possibly</td>
<td>37% in one series vs. 13% controls</td>
<td>no</td>
<td>one study only; mild, no clinical consequence</td>
</tr>
</tbody>
</table>

believed to trigger various cellular responses leading to cystogenesis and cyst expansion. Among the identified mechanisms are cAMP-mediated, cystic fibrosis transmembrane conductance regulator-dependent apical chloride secretion into the cyst lumen. The resulting cystic fluid accumulation, along with cAMP-dependent proliferative signals through PKA-, Src-, B-Raf or ERK, lead to metaplasia of cyst lining epithelia and cyst expansion [8]. Other pathways that utilize cAMP as a second messenger, including vasopressin V2-receptor and somatostatin SSTR2-receptor signaling, are present in renal tubular epithelia and have become targets for therapeutic approaches aiming at reducing intracellular cAMP. It is important to highlight that vasopressin V2-receptor signaling increases cAMP, in contrast to somatostatin SSTR2-receptor signaling that decreases cAMP. Therefore, the first utilizes an antagonist (i.e. tolvaptan) and then later an agonist (i.e. somatostatin) in order to achieve the desired suppression of intracellular cAMP. Proliferative phenotypes can also be activated by non-cAMP-dependent mechanisms: STAT3 and STAT6 proteins were found phosphorylated in cyst lining epithelia and are inappropriately activated in cystic tissue [9]. Further, many components of the mTOR-signaling axis have been found phosphorylated in cyst lining epithelia and adjacent renal tubules, indicating pathway activation and potential candidacy for pharmacologic intervention [10].

**PKD Progression and Outcomes**

ADPKD is characterized by progressive kidney cyst growth, resulting in renal parenchymal loss and hemodynamic changes through activation of the renin-angiotensin-aldosterone system. About 50% of patients with PKD type I will reach ESRD by the 6th decade of life, while patients with type II disease develop ESRD about 20 years later. Clinical symptoms alone are not a good indicator of disease activity or progression. Early onset of gross hematuria in teenage years and recurrent episodes of hematuria are indicators of a more rapid progression towards ESRD. Pain occurs in about 60% of the ADPKD population, but the pattern and severity of pain does not correlate well with the level of renal function impairment. Although those with larger sized kidneys generally have more pain than those with smaller kidney volume, the correlation is weak. Serum creatinine and estimated glomerular filtration rate (eGFR) are generally useful for the clinical classification of the stage of chronic kidney disease. However, in PKD patients, eGFR is typically well preserved over many decades of PKD progression, followed by a rapidly accelerated phase of eGFR decline. Therefore, eGFR is problematic for PKD staging and risk stratification, and may only be useful as a biomarker in the later stages of disease. MRI-based assessment of total kidney volume (TKV) has been validated as a reliable surrogate marker for eGFR change over time. The relationship of patient age, eGFR and TKV was demonstrated in a landmark study by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) [11, 12]. Changes in height-adjusted TKV (htTKV) via MRI correlated with a decline in iohalamate clearance. The rate of TKV increase was found to be a function of baseline htTKV (larger TKV, more rapid disease progression) and independent of patient age. While the rate of GFR decline was found to be mild over a wide range of TKV, a significantly accelerated decline in GFR was observed once a TKV of >1,500 ml was reached. TKV should thus be regarded as a reliable biomarker for disease progression.

**Current Therapeutic Approaches**

Cysts are the disease, and specific therapies targeted to prevent or delay progression of PKD are under investigation. Current state-of-the-art therapy for PKD is focused on quality treatment for chronic kidney disease: optimization of cardiovascular risk factors, blood pressure control, treatment of hyperlipidemia, low sodium/low protein diet, anemia management, secondary hyperparathyroidism therapy, ESRD counseling and transplant evaluation. PKD-specific therapies address cyst-related pain, management of cyst hemorrhage, cyst infections and understanding the basis for an increased incidence of uric acid nephrolithiasis.

Although not targeting the causative mechanisms of cyst formation and growth, the HALT-PKD study (NCT00283686) examined the effects of dual blockade of the renin-angiotensin-aldosterone system and aggressive blood pressure control on the rate of progression of ADPKD [13]. It represents the largest and longest randomized, multicenter trial ever conducted in ADPKD. One unique aspect of this study is the primary study endpoint of TKV, uniformly assessed every 2 years by MRI. HALT-PKD also entails a unique collection of clinical outcome data and biological materials, including genome analysis, allowing for future genotype-phenotype correlation studies. Part A of HALT-PKD enrolled 558 patients with a GFR of ≥60 ml/(min × 1.73 m²), while part B examined 486 patients with a GFR between 25 and 59 ml/
Based on this, the TEMPO 3 trial was designed as a study of intracellular cAMP and therefore of therapeutic interest in the context of PKD. Somatostatin analogues such as octreotide, pasireotide and lanreotide have been investigated in a number of smaller prospective randomized trials (NCT00309283, NCT00426153, NCT01354405 and NCT00309283). In small cohorts and short time intervals, there is a positive effect at slowing the growth rate of liver and kidney [17]. Medications are given as injections, and notable side effects are injection site pain, diarrhea, abdominal cramps and gas.

The ALADIN study (NCT00309283), a randomized, multicenter, single-blinded, placebo-controlled trial, assessed the effects of monthly-injected somatostatin analogue with long-acting release over a 3-year period (n = 79) [18]. Although a statistically significant reduction of TKV increase was seen at the 1-year follow-up (octreotide long-acting release: 46.2 ml vs. placebo: 143.7 ml, p = 0.032), no statistical significance was detected at the 3-year time point (octreotide long-acting release: 220 ml vs. placebo 454.3 ml, p = 0.25). Another recent publication found evidence of additive effect on cyst progression with tolvaptan and pasireotide in a hypomorphic PKD1 mouse model (Pkd1 RC/RC). The mice were treated from 1 to 6 months; both single-drug arms showed significant reduction of cyst progression, while the combination treatment arm evidenced an even greater reduction in cyst growth. While combination therapy significantly reduced fibrotic and cystic volumes, as measured by morphometric analysis, the cAMP levels were even decreased to those of wild-type animals [19]. Since tolvaptan-related hepatotoxicity was a major concern in the TEMPO trial, the possibility of treatment with reduced-dose tolvaptan in combination with somatostatin analogues may revive this therapeutic approach. It may allow patients to benefit from dual-pathway cAMP suppression, while keeping side effects at a minimum, but will certainly need to be investigated in human studies first.

mTOR Pathway

Studies evaluating mTOR pathway inhibition have not shown promising results from everolimus- or sirolimus-based treatment. The SIRENA trial (randomized, crossover study) showed a mild reduction in the TKV increase rate over a 6-month period, and the Everolimus in ADPKD trial had similar results over a 2-year period, but statistical significance was not reached [20, 21]. In both studies, baseline TKV was high (1,800 ml and 2,000 ml, respectively), and baseline GFR was between 55 and...

Vasopressin and Somatostatin Receptors and cAMP-Dependent Signaling

The main goal of targeting vasopressin and somatostatin pathways is reducing intracellular cAMP levels, consequently downregulating cyst growth and disease progression. This hypothesis was validated by pharmacologic and genetic disruption of vasopressin signaling, reversing PKD phenotypes in rodent disease models [14]. Based on this, the TEMPO 3:4 trial was designed as a multicenter, placebo-controlled, double-blinded trial investigating TKV progression, PKD complications and drug safety. Among patients who received tolvaptan for 3 years, the TKV increase was less rapid, the decline in kidney function was slower and there were less frequent PKD-related complications, like kidney pain. However, therapy was not well tolerated, and 8.3% of patients in the treatment arm had severe tolvaptan-related aquaresis leading to drug discontinuation. Clinically significant increases in liver enzymes occurred in 4.9% of the patients on tolvaptan. After discontinuation of tolvaptan, TKV progression resumed at the previous rate from before therapy [15]. Using tolvaptan off-label for the treatment of PKD can therefore not be supported.

It has been suggested that suppression of ADH secretion by free water intake should produce favorable results. A pilot study demonstrated that the urine cAMP correlated with urine osmolality changes in ADPKD patients during an acute water loading experiment, while 24-hour urine cAMP did not change with sustained water loading [16]. Whether increased free water intake would translate into a meaningful therapy is unknown and is being assessed in a long-term study.

The somatostatin SSTR2 receptor signaling pathway is also cAMP dependent (activation leads to suppression of intracellular cAMP) and therefore of therapeutic interest in the context of PKD.
75 ml/(min × 1.73 m²). In contrast, patients enrolled in the SUISSE ADPKD trial had an average baseline TKV of 1,000 ml and GFR of 92 ml/(min × 1.73 m²); the rates of TKV increase between the sirolimus and placebo arms were identical over an 18-month period [22]. None of the studies showed a therapeutic benefit regarding GFR preservation versus the placebo arms. The short duration of the studies and different baseline characteristics pose a challenge in drawing any significant conclusions about the utility of mTOR inhibition at this point. It is also noted that therapy-specific side effects, like immunosuppression, diarrhea, acne and mucositis represent a significant concern and a cause for dropout from the studies. mTOR inhibitors are not recommended for the therapy of ADPKD in the current formulation.

Whether metformin may confer a therapeutic benefit to PKD patients through indirect inhibition of the mTOR pathway by AMP-activated protein kinase (AMPK) has not been evaluated in a prospective study. Metformin-induced AMPK activity results in a reduction of cystic fibrosis transmembrane conductance regulator channel activity, therefore having dual positive effects on PKD-related signaling mechanisms. While in vitro and ex vivo models of cyst growth suggest a benefit from metformin, evidence for a therapeutic utility in humans is lacking [23].

**Growth Factor and Cytokine Signaling Pathways**

Cell proliferation and cell cycle modifying pathways can affect cystogenesis, particularly through inhibition of ERB, Src, CDK and STAT3/STAT6 signaling. Promising results have been noted with the CDK inhibitor, roscovitine. It produced a sustained effect after one administration, halting progression of cystic kidney disease in two mouse models [24]. EGF signaling has been linked to cystogenesis, and its inhibition by EKI-785 or EKB-569 slowed the progression of PKD in one rat model. SKI-606, also known as bosutinib, is a Src-kinase specific inhibitor that has been shown to interfere with renal cyst formation in two rodent models of PKD [25] and has recently entered a phase II randomized clinical trial (NCT01233869). Similarly, an experimental drug called KD019 is under investigation in a phase Ib/IIa trial in ADPKD patients (NCT01559363). KD019 (previously XL647) is a multi-specific inhibitor of a number of cytoplasmic and receptor tyrosine kinases, simultaneously targeting EGFR, HER2, Src, VEGFR and EphB4R, while having weak activity against other kinases, and has so far only been studied in the context of non-small-cell lung cancer [26, 27]. Finally, preliminary experimental data on curcumin and pyrimethamine suggest activity against STAT3 and STAT6 signaling in laboratory models of PKD, but more research including human study data need to be obtained in order to establish their true therapeutic potential [28, 29].

**Statins**

Statins are well-tolerated drugs, have many beneficial effects on endothelial dysfunction and left ventricular mass, and have been shown to reduce the severity of cystic disease in rat models of ADPKD [30]. The only human study analyzing the effect of pravastatin in ADPKD was a recently published randomized, double-blind, placebo-controlled trial on pediatric patients and young adults: a total of 110 participants were randomized to receive pravastatin or placebo for 3 years. Primary outcomes were a 20% change in hTKV, left ventricular mass index and microalbuminuria. The adjusted hTKV change was significantly decreased over the time period (pravastatin: 23% vs. placebo: 31%, p = 0.02). No statistically significant change was noted for left ventricular mass index (25 vs. 38%, p = 0.18) or microalbuminuria percent change (47 vs. 39%, p = 0.50) [31]. It needs to be emphasized that the median TKV and hTKV upon enrollment were about 450 ml and 280 ml/m, respectively, while patients in many adult intervention studies have baseline volumes of >1,000 ml and >700 ml/m. The definitive mechanism of pravastatin in the reduction of cyst growth remains elusive, and more research will be necessary to investigate the effects of statin therapy in the adult ADPKD population. Although not FDA approved for ADPKD treatment, the good tolerability of pravastatin and the potentially favorable risk-benefit ratio may justify its off-label use, if individual patients and physicians desire.

**Conclusion**

PKD is one of the most common monogenic disorders in humans. It is characterized by the formation and inevitable expansion of kidney cysts, ultimately leading to ESRD. Current therapeutic approaches focus on symptom and complication management, as well as slowing the rate of disease progression. Recent advances in genetics and new insights into the molecular pathways of cystogenesis will eventually lead to novel thera-
pies, targeting the very mechanisms of cyst formation and expansion. The just published HALT PKD study has demonstrated that blockade of the renin-angiotensin-aldosterone axis and aggressive blood pressure lowering decreases cyst growth and lessens left ventricular mass index in the PKD population, but a change in the eGFR slope of decline did not reach statistical significance with treatment.

**References**


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**Disclosure Statement**

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