Chapter 6

Clinical Trials in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Autosomal dominant polycystic kidney disease is the most common life-threatening genetic disease, affecting 1/400 to 1/1000 live births. It represents the 4th leading cause of end-stage kidney disease and accounts for 13% of kidney transplants in the United States. It is characterized by irreversible cyst growth leading to progressive parenchymal damage. Despite promising results, there is currently no Food and Drug Administration approved therapy to cure or slow the progression of the disease. The growing understanding of the

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pathophysiological mechanisms leading to cyst formation and growth has led to the development of several therapeutic agents, some with very promising results. In this chapter, we will review the past and ongoing clinical trials that explored these specific targets, focusing mainly on drugs targeting the cyclic adenosine 3',5'-monophosphate pathway (vasopressin V2 receptor antagonists and somatostatin analogs), mammalian target of rapamycin (mTOR) inhibitors and renin-angiotensin blockade. We will discuss novel therapeutic targets currently being explored in pilot clinical studies, including high dose niacinamide, tyrosine kinase inhibitors and others. Given its slowly progressive nature and lack of early sensitive biomarkers, clinical trials are limited by the need for long follow-up periods to assess the beneficial effect on kidney function of any therapeutic intervention. There is a growing need of new biomarkers of PKD progression to help accelerate the progress of clinical trials in this field. We will finally explore the current accepted and candidate biomarkers in PKD and discuss current challenges to the development of clinical trials in PKD.

Key words: Clinical trial; Drug therapy; Glomerular filtration rate; Kidney volume

Introduction

The genes for autosomal dominant polycystic kidney disease (ADPKD), PKD1 and PKD2 encoding polycystin-1 (PC1) and polycystin-2 (PC2), respectively, were first identified 20 years ago (1-3). In the intervening years a vast amount of information has emerged regarding the cellular mechanisms and signaling pathways that are dysregulated in PKD, and numerous potential targets and candidate drugs have been proposed (4), but as yet there is no drug approved in the United States for treating the disease. Thus, PKD is "therapy-ripe" and represents a very exciting area for clinical trials. The first 8 interventional trials in PKD have been published in the past five years (Table 1) and we are poised for a deluge of novel drugs and other therapeutic candidates that will need to be tested.

Challenges in drug development and the design of clinical trials in ADPKD

A number of challenges are faced by investigators attempting to bring therapies to clinical trials and ultimately obtain regulatory approval.

Preclinical models may not predict clinical efficacy

The pathogenesis of PKD is complex and still poorly understood. It is fairly well accepted that renal tubule epithelial cell proliferation is increased, and that there is

abnormal secretion of fluid into the lumen. Thus, assays of PKD cell proliferation (5) and of cyst growth from PKD cells in 3D culture (6) have been used to test drugs. However, existing PKD cell lines and primary cells all have their limitations and so it is unclear if in vitro assays truly predict clinical drug efficacy. Rodent PKD models are widely used for preclinical testing but they do not completely mimic the human disease (7). Most require homozygous gene deletion from birth or early embryonic life, and then exhibit an accelerated disease progression with numerous cysts developing contemporaneously. By contrast PKD patients are heterozygous and have a slowly progressive disease with cysts of varying ages emerging over several decades of life (8). Moreover, in nonorthologous models that do more closely mimic the human disease (e.g. pcy mouse, or Han:SPRD-cy rat) it is unclear whether the underlying disease mechanism is the same as that for ADPKD. Finally, the rodent kidney is several orders of magnitude smaller and is simpler in structure than the human kidney, so the mechanical effects of cysts on normal kidney tissue may not be faithfully modeled. Some of these limitations will hopefully be overcome with the development of hypomorphic (9) or delayed-onset disease models (10), and large animal models (11).

Difficulty in assessing biological efficacy

In early phase trials, a critical component is determining whether the drug, at the dose and route given, has the intended pharmacodynamic effect on its target in the cystic kidney, for proof of biological efficacy. If the drug has a measurable physiological effect (for example, tolvaptan causing a reduction in urine osmolality) this can be used, but such a convenient readout is unlikely to be available for most drugs. Another possibility is to employ a biomarker that is informative of the drug effect. For technical and ethical reasons cystic kidneys are not generally biopsied. Thus the only practical way to access information about intrarenal biochemical events is to sample soluble factors, cells or exosomes that are excreted in the urine. However, the urine also contains small molecules and peptides filtered from the circulation, as well as cells and probably exosomes shed from the lower urinary tract, diluting the signal of interest. Many intracellular signaling molecules that might be drug targets are not found in urine at all. Finally, cyst fluid, which contains factors secreted from cyst epithelium is usually sealed within large non-communicating cysts and not in continuity with the tubular fluid of functioning nephrons, leaving only the younger and smaller communicating cysts to deliver relevant molecules into the urine.

The use of mammalian target of rapamycin (mTOR) inhibitors for ADPKD illustrates this challenge well. While mTOR inhibitors at high doses were shown to be effective at treating PKD in mice (12, 13), their use in humans, at the usual doses used for immunosuppression and that were known to be well tolerated, showed equivocal or no clinical efficacy in

retarding progression of ADPKD (14, 15) (see detailed discussion below). However, in these studies there was no determination of whether the mTOR pathway in the epithelium of kidney cysts or precystic tubules was effectively inhibited, presumably because there are no urinary biomarkers of this pathway. A fortuitous occurrence in a patient in France provided evidence to suggest that the usual clinical doses of mTOR inhibitors are insufficient to achieve biological efficacy within the PKD kidney (16). This patient was inadvertently transplanted with an ADPKD kidney, given sirolimus for post-transplant immunosuppression and then underwent a routine kidney biopsy at 1-year post-transplant. In peripheral blood mononuclear cells from the patient, phosphorylation of p70 S6 kinase by mTOR was effectively inhibited by sirolimus, confirming that there was a systemic drug effect. However, the kidney biopsy from the same patient showed persistently high levels of both phospho-S6 ribosomal protein and phospho-4E-BP1, indicating absence of biological efficacy of sirolimus within the kidney.

Long natural history of disease

In ADPKD, cysts likely begin forming before birth (17) and grow exponentially throughout the life of those kidneys (18), a duration that averages about six decades (19). During this time, cysts progressively compress and injure neighboring structures, including tubules and vasculature, and incite inflammation and eventually fibrosis. However, the glomerular filtration rate (GFR) remains well-preserved for several decades, likely due to compensatory hyperfiltration of the remaining functional nephron units. Thus, clinical trials are likely to show the greatest therapeutic benefit in early adulthood (or perhaps even in childhood), when most of the damage from cyst growth is being inflicted and is reversible (20). However, at this stage in the disease it is difficult to demonstrate any improvement in the course of the GFR and virtually impossible to assess the rate of progression to end-stage kidney disease (ESKD). This highlights one of the limitations of using improvement in GFR as a measure of drug clinical efficacy (others are discussed in the next two subsections). By the time the GFR begins to decline, there is already extensive kidney fibrosis, there has presumably been so much nephron dropout that the remaining nephrons can no longer compensate adequately, and the kidneys are set on a course of rapid and likely irreversible decline that usually leads to ESKD within a few years. A trial of therapy at this late stage is unlikely to alter the natural history of the disease.

Age-related decline in GFR

GFR declines slowly with age even in normal individuals, with an average slope of approximately -0.8 mL/min/1.73 m^2 (21, 22). Thus, the slope of GFR in ADPKD patients

represents the additive effect of two processes: cyst growth-induced kidney injury, which is the target of our therapy, and age-related GFR decline, which presumably would not be ameliorated by PKD therapy. This limits the magnitude of the improvement in GFR slope that we could reasonably expect to see in a clinical trial.

Acute effects of drugs on GFR

A number of drugs have acute hemodynamic effects on GFR that differ from, and mask their long-term effect, on kidney function (23, 24). For example, drugs that block the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor AT1 blockers (ARB) cause vasodilation of the glomerular efferent arterioles and acutely reduce GFR. However this same effect ameliorates glomerular hypertension and contributes to the long-term effect of these drugs to reduce the slope of decline in GFR (25). In a study in which the outcome is the slope of GFR measured from the start of the trial, before drug treatment is initiated, to the end of the trial while on-drug, the short-term detrimental effect may partially or totally mask the long-term beneficial effect. A similar effect is seen simply with marked lowering of the blood pressure (BP) and probably accounts for the lack of beneficial effect of a low BP target as compared to a standard BP target on the overall slope of the GFR in the HALT A trial (see detailed discussion below) (26).

This phenomenon can be addressed by modifying the study design. In the TEMPO 3:4 study (see detailed discussion below), it was anticipated that the vasopressin receptor-2 antagonist tolvaptan would have a similar hemodynamic effect. The study was therefore designed so that the slope of reciprocal creatinine (a secondary outcome that was used as a surrogate for GFR) was determined "on-drug", starting after the drug had been titrated to its target dose, and ending with the last encounter in which the patient was still taking the drug (27).

Lack of sensitive early clinical biomarkers acceptable to the FDA as endpoint

Given the aforementioned limitations of using GFR or ESKD as endpoints in clinical trials of ADPKD, much effort has focused on identification of alternative clinical biomarkers that are closely associated with the rate of disease progression and predictive of the rate of future kidney function decline. The best biomarker to date is the total kidney volume (TKV). TKV (often adjusted for height and abbreviated as htTKV) has the merit of being a direct readout of cyst growth, which is the essence of the disease. TKV increases exponentially at a rate that is unique for each patient and averages 5% per year across the ADPKD population (18). The TEMPO 3:4 study provided the first evidence that the rate of

increase of TKV could be reduced by a drug and that this was associated with a salutatory effect on the rate of decline of kidney function (27). In the United States, TKV is not currently accepted by the Food and Drug Administration (FDA) as an outcome for the purposes of drug approval. However, the FDA did recently issue a Letter of Support for the use of TKV as a prognostic biomarker for enriching for patients with more rapidly progressive disease in clinical trials.

Long-term tolerability needed for drug acceptability

Finally, because the pathogenesis of ADPKD involves abnormal cell proliferation, resembling a benign neoplasm (28), many drugs currently in development for this disease are repurposed cancer therapies (29, 30). However, anticancer drugs are usually administered for short durations and, because of the acute life-threatening nature of the disease, even substantial toxicity can be considered acceptable. By contrast, therapy for ADPKD would likely need to be lifelong, and start when the patient is young and asymptomatic, so the bar in terms of drug tolerability and safety has to be set very high. This should influence the design of any clinical trial and the overall development strategy.

Ongoing or recently completed clinical trials of therapy

B*lood pressure and the renin-angiotensin system*

Hypertension is an early and major manifestation of ADPKD and is associated with accelerated progression to ESKD as well as increased cardiovascular morbidity and mortality (31, 32), as it is in other kidney diseases. Activation of the renin-angiotensin-aldosterone system (RAAS) has been shown to be a major contributor to the hypertension of ADPKD (33). There is also some evidence to suggest that the RAAS might directly promote cyst growth (34, 35), perhaps via its mitogenic effects. Inhibitors of RAAS such as ACEI are already standard of care for the treatment of hypertension in chronic kidney disease (CKD), but suppression of RAAS is incomplete. This is due to the existence of non-ACE pathways for angiotensin II generation, such as chymase, which has been shown to be upregulated in ADPKD (36). Thus, addition of an ARB to ACEI could potentially suppress the RAAS further.

To test these hypotheses, the Halt Progression of Polycystic Kidney Disease (HALT-PKD) Study Group designed two National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)-sponsored concurrent, multi-center, randomized controlled trials (RCT), the HALT study A of 558 ADPKD patients with early disease (estimated GFR by the

MDRD equation, eGFR > 60 mL/min/1.73 m^2), and the HALT study B of 486 patients with late disease (eGFR 25-60 mL/min/1.73 m^2) (37). Study A tested whether low BP control (95 to 110/60 to 75 mm Hg) would delay progression of kidney disease compared to standard BP control (120 to 130/70 to 80 mm Hg), and both study A and B tested whether combination therapy with an ACEI and ARB (lisinopril + telmisartan) would delay progression of kidney disease compared to ACEI monotherapy (lisinopril + placebo).

In Study A (26), the primary outcome, the annual rate of growth of TKV, was 14.2% slower in the low BP group compared to the standard BP group (5.6% vs. 6.6%, p=0.006). The overall change in the eGFR over the course of the study was no different between the groups. A pre-specified analysis of the short-term (0-4 months) and long-term (>4 months) effects showed that the low BP group as compared to the standard BP group experienced a short-term decline in eGFR after starting treatment (−3.1 vs. 0.5 ml/min/1.73 m^2 per 4 months, P<0.001) which masked a beneficial effect on the slope of the eGFR in the long-term phase that reached marginal statistical significance (−2.7 vs. −3.1 ml/min/1.73 m^2 per year, respectively; P = 0.05). The low BP group had slightly more dizziness and light-headedness but no other adverse effects.

In both Study A and Study B (26, 38), there was no additional benefit of combination therapy with ACEI and ARB, as compared to ACEI monotherapy. This is consistent with several recent studies in other conditions that have shown that any benefits from dual blockade of the RAAS are outweighed by increased incidence of hypotension, AKI and hyperkalemia (39-41). Importantly though, in HALT-PKD combination therapy with an ACEI and ARB was not associated with excess adverse events, showing that combination therapy can be administered safely if needed in this population.

Vasopressin V2 receptor antagonists

Cyclic adenosine-3',5'-monophosphate (cAMP) plays a major role in driving cyst growth in PKD, by stimulating both fluid secretion and cell proliferation in cyst-lining epithelial cells (42). ADPKD cysts largely originate from the collecting duct, a nephron segment that expresses vasopressin V2 receptors (V2R) which signal through GS, adenylate cyclase and generation of cAMP. Thus, vasopressin, signalling through V2R, accelerates cyst growth. Moreover, one can surmise that cAMP is probably an early and central node in the signaling cascade that drives cyst growth because when Brattleboro rats that have genetic absence of vasopressin were bred with a strain of rats with polycystic kidneys (PCK), cystogenesis was almost completely inhibited (43). V2R antagonists have been tested in a number of rodent PKD models and found to be effective at retarding disease progression in all of them (44-46).

Based on these findings tolvaptan, a V2R antagonist already clinically approved for the treatment of hyponatremia, was tested in ADPKD. The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial was a multicenter, double-blind RCT (27). 1445 patients with ADPKD with a TKV of >750 mL and estimated creatinine clearance >60 mL/min were randomized to tolvaptan or placebo and followed for 3 years. The annual rate of change of TKV was reduced by half by tolvaptan, from 5.5% to 2.8%. Tolvaptan treatment was associated with a slower decline in kidney function (eGFR slope of −2.72 ml/min/1.73 m^2/yr in the tolvaptan group versus −3.70 in the placebo group). Patients on tolvaptan had more adverse events related to increased aquaresis (thirst, polyuria, nocturia, and polydipsia), and 8% of patients in the treatment group discontinued the trial drug for this reason. More patients who received tolvaptan than those who received placebo (4.9% vs. 1.2%) had elevations of alanine aminotransferase to greater than 2.5 times the upper limit of the normal range. However, due to the design of the TEMPO 3:4 trial, the effects of tolvaptan on patients with more advanced ADPKD are not available.

In summary, tolvaptan convincingly slowed down ADPKD disease progression and reduced the rate of decline in eGFR by 1 ml/min/1.73 m^2/yr which might be expected to delay the onset of ESRD significantly. Unfortunately, tolvaptan was poorly tolerated by some patients, and the increased incidence of abnormal liver function tests raised some concern that there might be a risk of serious hepatotoxicity associated with its use.

Largely on the basis of TEMPO 3:4, tolvaptan has now been approved for treatment of ADPKD in Japan, Canada and Europe. In the US, tolvaptan was not approved by the FDA. However, Otsuka is sponsoring another trial, REPRISE, which will be conducted under FDA guidance and will recruit patients with more advanced stages of CKD with the goal of obtaining more accurate estimates of the treatment effect on decline in kidney function and the incidence of hepatotoxicity.

Somatostatin analogs

Somatostatin is a peptide inhibitory hormone that signals via somatostatin receptors to inhibit the generation of intracellular cAMP. Somatostatin receptors are expressed in the kidney and liver, so somatostatin analogs might be expected to ameliorate cyst progression in both the kidney and the liver in ADPKD patients. In the ALADIN trial (A Long-Acting somatostatin on DIsease progression in Nephropathy due to ADPKD), 79 patients with eGFR >40 ml/min/1.73 m^2 were randomized to receive, every 4 weeks, injections of octreotide-LAR, a synthetic analog of somatostatin encapsulated into microspheres for

long-acting release, or placebo injections, and were followed for 3 years (47). After 1 year, the increase in TKV was reduced by 2/3 with octreotide compared to placebo (p=0.032). Over the entire 3-year duration of the trial, the increase in TKV in the octreotide group was half that of the placebo group, but this was no longer statistically significant. This suggests either that the treatment effect is attenuated over time, or simply that the sample size was too small. 10% of patients treated with octreotide developed cholelithiasis or acute cholecystitis, raising concerns about its safety with long-term use.

Larger trials of somatostatin analogs are clearly needed. ALADIN 2 is an ongoing Phase 3, double-blind, placebo-controlled RCT being conducted in Italy with a planned recruitment of 98 patients. The design is similar to that of ALADIN except that patients with eGFR of 15-40 ml/min/1.73 m^2 are being enrolled, presumably to select for patients with rapidly declining GFR that might benefit more from the treatment. DIPAK 1 is a Phase 3 RCT in 300 patients conducted in the Netherlands that will compare open label lanreotide, administered subcutaneously every 4 weeks, with standard care (48).

Mammalian target of rapamycin (mTOR) inhibitors

The cytoplasmic tail of polycystin-1 has been shown to interact with tuberin, and the mTOR pathway is inappropriately activated in cyst-lining epithelial cells in ADPKD (49). Inhibitors of mTOR are widely used clinically as immunosuppressants. In several rodent models of PKD, mTOR inhibitors have been shown to ameliorate the disease (13, 49-51). However, the clinical trials of mTOR inhibitors have been disappointing.

Walz et al. randomized 433 patients with ADPKD and an average eGFR of 53-56 ml/min/1.73 m^2 to receive the mTOR inhibitor, everolimus, or placebo in a double-blinded fashion, and then followed them for 2 years (14). The increase in TKV at 1 year was reduced by about 1/3 in the everolimus group compared to placebo. There was a similar reduction at 2 years but it was no longer significant. Despite the improvement in kidney volume, eGFR declined faster in the everolimus group than in placebo (5.5 ml/min/1.73 m^2 vs. 3.5 ml/min/1.73 m^2 respectively, $p<0.001$). The reason for this is unclear, but a number of possibilities have been proposed. First, the mTOR pathway mediates glomerular hypertrophy and hyperfiltration, thus maintaining GFR after nephron loss, so everolimus may have deprived the kidneys of this compensatory mechanism. Second, short-term changes in GFR do not necessarily correctly predict long-term changes and so 2 years of follow-up is probably too short to ascertain the true long-term trend. Indeed, if glomerular hyperfiltration is harmful in the long term, then it would be predicted that amelioration of hyperfiltration would reduce the decline in GFR given sufficient follow-up time. Third, as more patients on everolimus experienced edema and needed diuretics, this might have worsened kidney function. Finally, the selection of a patient population with relatively

advanced CKD and probably significant fibrosis and irreversible kidney injury may have obscured any potential benefit conferred by everolimus (52).

In a smaller, open label trial, Serra et al. randomized 100 patients to receive sirolimus or placebo (15) and found no difference in the rate of increase of TKV. The study was not powered to assess kidney function and so not surprisingly, eGFR did not differ significantly between the groups.

An additional consideration is that inability to administer sufficient dosage to achieve biological efficacy may have accounted for the lack of clinical efficacy of the mTOR inhibitors, as compared to the preclinical studies. As discussed earlier, the study by Canaud et al. suggested that sirolimus dosed as an immunosuppressant post-transplant is inadequate to inhibit mTOR activity in PKD cysts (16). However, higher doses are unlikely to be achievable. In the study by Walz et al. (14), one third of patients did not complete the study because of drug-related adverse events, including proteinuria which might adversely affect kidney function in the long-term. In the study by Serra et al. (15), the drug dose was lower than intended because of dose-limiting side-effects.

High water intake

Given the importance of vasopressin in the rate of cyst growth, it has been suggested that simply increasing water intake would be sufficient to suppress vasopressin secretion, and hence retard disease progression in ADPKD (53). Studies in PCK rats confirmed that increasing water intake by 3.5-fold retarded cyst growth and the decline of kidney function (54). Wang et al. developed a simple clinical method based on a measurement of urine osmolality to estimate the amount of additional water that should be ingested (55). However, many nephrologists are already recommending that their ADPKD patients empirically increase their fluid intake. The practice is widespread in the community, thus making it challenging to test the efficacy of high fluid intake in a randomized controlled trial. The only clinical study of high water intake that has so far been conducted was by Higashihara et al. They assigned 30 patients to high and free water-intake groups based on patient preference, and found that the slope of TKV and eGFR were worse in the high water intake group (56). However, the study was flawed because of the non-randomized assignment to the different groups, and was much too small to reach any meaningful conclusions.

Other therapies

Statins, or 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, have pleiotropic effects, including inhibiting farnesylation and activation of the monomeric

GTP-binding protein, Ras, and hence inhibiting cell proliferation (57). Statins have been shown to be effective in preclinical models of PKD (35,58). In a placebo-controlled RCT conducted in 110 children with ADPKD, pravastatin was shown to reduce the change in htTKV over 3 years (23% vs. 31%) (59). This is notable for being the first substantive therapeutic trial in ADPKD to be conducted in children.

The epidermal growth factor (EGF) receptor is overexpressed and mislocalized to the apical membrane in autosomal dominant and recessive forms of PKD (60, 61). Tyrosine kinase inhibitors that block EGF receptor catalytic activity and downstream mitogenic signaling appear to be effective at retarding disease progression in rodent PKD models (62, 63). Two tyrosine kinase inhibitors are currently undergoing early phase clinical trials in ADPKD (Table 1). A concern with this approach is that this antiproliferative strategy may not be sufficiently specific for PKD cyst epithelium and hence would have significant adverse effects in other proliferating tissues. While such side-effects might be acceptable in a drug being developed for short-term treatment of a life-threatening malignancy, tolerability is a major concern in a drug being developed for treating asymptomatic young adults with ADPKD over a large duration of their lifetime.

Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide–dependent protein deacetylase that was recently found by Zhou et al. to be a novel pathway responsible for cyst growth (64). SIRT1 was shown to promote cyst growth by deacetylation and increased phosphorylation of retinoblastoma protein which becomes inactive, enabling transcription of genes that mediate entry into the S-phase of the cell cycle (65) and also by inhibition of apoptosis via deacetylation of p53 (66), an important tumor suppressor protein. By promoting a base-exchange reaction at the expense of deacetylation, niacinamide serves as a noncompetitive inhibitor of SIRT1 (67). Niacinamide (also known as nicotinamide) is a water-soluble amide derivative of nicotinic acid (also known as niacin) and these two molecules represent the two major forms of vitamin B3. Administration of either high-dose niacinamide, a pan sirtuin inhibitor, or EX-527, a SIRT1-specific small-molecule inhibitor, delayed cyst growth and improved kidney function in two orthologous mouse models of ADPKD (64).

The dose of niacinamide that would likely be needed for clinical efficacy in ADPKD is 30 mg/kg/day (compared to the recommended daily dietary allowance of vitamin B3, which is 14 to 16 mg/day). Fortunately doses of niacinamide of this magnitude have already been tested both in adults and in children over 3 years and found to be safe (68). Niacinamide is classified as a dietary supplement, so if it is found to be effective in the treatment of ADPKD, it would not need approval by the FDA, and would be widely available to ADPKD patients at very low cost. Because of this, niacinamide is being tested in two early

phase clinical trials at the University of Kansas Medical Center (KUMC). These trials are designed to assess biological efficacy, as determined by the level of phosphorylation of Rb and acetylation of p53 in peripheral blood mononuclear cells, to estimate the clinical effect in terms of reduction in the increment of htTKV at 1 year, and to assess the tolerability and safety of niacinamide in this population.

Triptolide is an active diterpene found in the traditional Chinese medicine, Lei Gong Teng. It has been shown to induce intracellular calcium release in a mechanism dependent on polycystin-2. By restoring calcium signaling it seems to inhibit PKD cell proliferation and delay cyst growth (69). In orthologous mouse models of ADPKD, triptolide delayed disease progression (70, 71). The only published clinical study was an open label trial of 9 patients with ADPKD and proteinuria >1 g/day, which is rather unusual in this disease (72). Triptolide appeared to reduce proteinuria in this uncontrolled study. An RCT of triptolide was initiated at Nanjing University School of Medicine (ClinicalTrials.gov Identifier: NCT00801268) but is currently reported as being terminated because of a high rate of drop-out. Another trial being conducted at Shanghai Changzheng Hospital is currently recruiting.

Future directions

Clinical testing of therapies in ADPKD presents a number of daunting challenges, particularly in the US. These include the long lead time of disease progression before GFR falls predictably, failure of the FDA to accept TKV as a surrogate endpoint for drug approval, and the cost of large-scale clinical trials. The following are recommendations and predictions for future directions that may best address these issues.

We urge continued emphasis on repurposing already-approved drugs and testing dietary supplements. These have the advantage that there is already some knowledge about their safety, thus dramatically reducing the risk and cost of their development. In addition, even if the clinical trial data fall short of meeting FDA criteria for approval for the indication of PKD treatment, it may be sufficient to convince the nephrology community to use a drug off-label (especially if it is inexpensive), or to use a dietary supplement off the shelf.

Along those same lines, we believe that diet could be a major determinant in PKD disease progression. This includes not only water intake, but also sodium intake (73) and the balance of acid and base equivalents (74). At KUMC we are completing a pilot study to test the feasibility and acceptability of a diet low in salt and animal protein and enriched infruits and vegetables, and its efficacy at reducing net acid excretion (NCT01810614).

Table 1. Summary of major interventional trials in ADPKD[1]

Intervention	Mechanism of action[2]	Trial name	Sponsor	ClinicalTrials.gov Identifier	Trial design[3]	Status and outcome	References
Standard vs. low BP control Lisinopril vs. lisinopril + telmisartan	ACEI + ARB	HALT A	NIDDK	NCT00283686	2x2 factorial RCT in patients with eGFR ≥ 60 mL/min/1.73 m^2	Completed	(26)
Lisinopril vs. lisinopril + telmisartan	ACEI + ARB	HALT B	NIDDK	NCT01885559	RCT in patients with eGFR 25-60 mL/min/1.73 m^2	Completed	(38)
Tolvaptan	V2 receptor antagonist	TEMPO3/4	Otsuka	NCT00428948	Phase 3, placebo-controlled RCT in patients with eGFR ≥ 60 mL/min/1.73 m^2	Completed	(27)
Tolvaptan	V2 receptor antagonist	REPRISE	Otsuka	NCT02160145	Phase 3b, placebo-controlled RCT in patients with late stage 2 to early stage 4 CKD	Recruiting	
Octreotide	Somatostatin analog	ALADIN	Mario Negri Institute for Pharmacological Research	NCT00309283	Placebo-controlled RCT in patients with eGFR ≥ 40 mL/min/1.73 m^2	Completed	(47)
Octreotide	Somatostatin analog	ALADIN 2	Mario Negri Institute for Pharmacological Research	NCT 01377246	Phase 3, placebo-controlled RCT in patients with eGFR 15-40 mL/min/1.73 m^2	Active, not recruiting	

Lanreotide	Somatostatin analog	DIPAK 1	University Medical Centre Groningen	NCT01616927	Phase 3, placebo-controlled RCT	Active, not recruiting	(48)
Lanreotide	Somatostatin analog	LIPS	Assistance Publique - Hôpitaux de Paris/IPSEN Pharmaceuticals	NCT02127437	Phase 3, placebo-controlled RCT	Recruiting	
Everolimus	mTOR inhibitor		Novartis	NCT00414440	Phase 3, placebo-controlled RCT	Completed	(14)
Everolimus	mTOR inhibitor		Wyeth	NCT00346918	Phase 3, placebo-controlled RCT	Completed	(15)
Pulsed sirolimus	mTOR inhibitor	RAP	Medical University of Vienna	NCT02055079	Placebo-controlled RCT	Recruiting	
Pravastatin	HMG-CoA reductase inhibitor		University of Colorado, Denver/NIDDK	NCT00456365	Phase 3, placebo-controlled RCT in children	Completed	(59)
Bosutinib	Tyrosine kinase inhibitor		Pfizer	NCT01233869	Phase 2, placebo-controlled RCT	Completed	
KD019	Tyrosine kinase inhibitor		Kadmon	NCT01559363	Phase 1b/2a uncontrolled dose escalation study	Recruiting	
Niacinamide	Sirtuin inhibitor	NIAC-PKD1	University of Kansas Medical Center	NCT02140814	Phase 2, open label, single arm	Active, not recruiting	

Niacinamide	Sirtuin inhibitor	NIAC-PKD2	NIDDK	Pending	Phase 2, placebo-controlled RCT	Recruiting	
Triptolide	Stimulator of calcium release		Nanjing University School of Medicine	NCT00801268	Open label RCT	Terminated	
Triptolide	Stimulator of calcium release		Shanghai Changzheng Hospital	NCT02115659	Phase 3, placebo-controlled RCT	Recruiting	
Renal sympathetic denervation		RAFALE	Shanghai Changzheng Hospital	NCT01932450	Phase 2, open label RCT	Recruiting	

[1]Studies were identified primarily from a search of the ClinicalTrials.gov database. Please note that this is not a comprehensive listing of all PKD trials. It includes primarily interventional studies where disease progression was an endpoint. Studies of patients that received kidney transplants, studies of effect on liver disease progression, observational studies, studies that were terminated and not published, and small early phase studies that were superseded by larger studies with more rigorous design are omitted.

[2]ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin AT_1 receptor blocker; mTOR, mammalian target of rapamycin; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A

[3]Specific details of study population are included only where needed to highlight the difference between two apparently similar trials.

Controlled trials that test the clinical efficacy of dietary intervention, while not particularly exciting, could have a major impact on the management of ADPKD.

Because ADPKD is a lifelong disease, we believe that early treatment has the greatest potential to change its long-term course and so treating children is likely to have the greatest benefit (20). Clinical trials are rarely conducted in children because of concerns about safety and ethics but they are certainly possible, and therapies such as niacinamide that have already been shown to be safe in children (68) could lead the way.

Because falling GFR is a late event in ADPKD and an indicator of irreversible, fibrotic changes within the kidney, earlier biomarkers of disease progression that reverse in response to effective therapy are badly needed. While a number of blood and urine biomarkers have been identified (75-81), none has yet been shown to have the sensitivity and reliability needed. One promising new area of biomarker discovery is that of urinary exosomes, which are a rich source of renal tubule epithelium-derived proteins and, particularly, of proteins that are complexed to the polycystins (82).

Another approach might be to test therapies in a cystic kidney disease with a more rapid and aggressive course. Because the pathogenesis of autosomal recessive PKD (ARPKD) closely resembles that of ADPKD, testing therapies in children with ARPKD, who generally have a rapid decline in kidney function in childhood, might enable one to see a change in the GFR slope early on. Even detecting a change in the incidence of a hard outcome, such as ESRD, might well be feasible. Moreover, ARPKD (unlike ADPKD) is unequivocally a rare disease and as there is also no currently approved treatment, any candidate drug would be considered an orphan drug and qualify for regulatory and financial incentives that would greatly facilitate its commercial development (83).

Rigorously designed and adequately powered late-stage trials to definitively prove the clinical efficacy of a therapy requires large numbers of patients and, particularly for off-patent drugs and for therapies that cannot be commercialized, such as dietary interventions and dietary supplements, the cost may be prohibitively expensive. Pragmatic trials that test therapies in real-world clinical settings using the existing infrastructure and protocols of standard care may allow such trials to be conducted at much lower cost and may even be better at predicting their real clinical effectiveness (84).

Conflict of interest

M.E. serves as a study investigator on clinical studies conducted at KUMC sponsored by Otsuka, Kadmon and Genzyme. F.T.W. has served as a study investigator on clinical studies conducted at KUMC sponsored by Otsuka.

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