Novel Treatments of Autosomal Dominant Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is considered the most common inherited form of kidney disease across all ethnic types (1–3). Present understanding holds that mutations of responsible genes, either *PKD1* or *PKD2,* occur during embryogenesis and variably combine with "second hit" mutations within renal tubular epithelial cells that alter the intracellular level of polycystins, leading to epithelial cyst formations early in life (2–6). Cyst pathogenesis includes disordered nephron epithelial cell proliferations resulting in regional nephron bulging, accelerated apoptosis, loss of epithelial cell polarity, epithelial cell dedifferentiation, and eventual "pinching off" of the altered nephron regions into isolated cysts (3,6). Vasopressin-mediated fluid transport into cysts coupled with direct stimulation of cystic growths are considered central pathogenic growth variables (2–4).

Ultimately, multiple cysts slowly expand through adulthood, compressing functioning nephrons and blood vessels and causing progressive loss of renal function. Inflammation and fibrosis accompany renal deterioration. Approximately 50% of affected individuals experience advanced kidney failure by age 60 years (3). Whether a patient is afflicted with PKD1 or PKD2 mutations, heterogeneity of somatic mutations and individual variables, such as high BP, hemorrhagic events, and infections, alter disease progression (3). Thus, ADPKD presents a significant effect on health care systems worldwide.

Pharmacologic targets for intervention are based on known pathogenic variables. In an experimental model of polycystic kidney disease (PKD), genetic knockout of vasopressin production yielded rodents that remained relatively free of cysts until a vasopressin receptor agonist was administered exogenously, and then cysts appeared (4). In similar animal models of genetic PKD showing progressive cyst growth, vasopressin interruption using V2 antagonists slows cyst formations and enlargement (7–9). Even forced-water ingestion sufficient to naturally suppress secreted vasopressin can slow cyst formation and enlargement (10). These observations led to emphatic recommendations that patients with ADPKD aim to ingest >3 liters of noncaffeinated fluid per day, with the hope that natural vasopressin suppression would attenuate cyst growth (11,12). In addition to vasopressin-mediated fluid transport into cysts, other studies have demonstrated that the disordered nephron epithelial cell proliferation is related to activation of mammalian target of rapamycin (mTOR), a protein kinase that regulates polycystin pathways, cell proliferation, and protein synthesis (13,14). In experimental models of ADPKD, mTOR inhibition slows cyst enlargement (13,14). Additional evidence has established that cAMP mediates the progression of cystic disease in ADPKD by stimulating nephron cell proliferation and vasopressin-mediated fluid transport into cysts (15–17) This provides rationale for therapies targeting cAMP, including somatostatin analogs, which can thwart renal and liver cyst growth in experimental models (17–19).

On the basis of emerging understanding of complex cellular pathogenic pathways for ADPKD, hope has emerged regarding clinicians' ability to modify the clinical course of ADPKD (3). For decades, ADPKD has been passively observed by the doctor. BP control has been deemed essential, as is avoidance of trauma, urinary stone formation, and infection, but little else could alter the biology of ADPKD or its clinical course. Routine cyst drainage or cyst decapitations proved of little help (20). Angiotensin inhibition has received emphasis as having unique benefit owing to known activation of the renin-angiotensin-aldosterone system in ADPKD (21–25). One well done study demonstrated that angiotensin-converting enzyme inhibition prevented decreased creatinine clearance over a 5-year period in children and young adults with ADPKD (25). Additional proof of unique benefit resides with final analysis of the HALT Progression of Polycystic Kidney Disease trial (26).

In this context, four novel therapies with strong molecular rationales have entered into clinical trials as potentially modifying ADPKD: vasopressin-receptor inhibitors, mTOR inhibitors, somatostatin analogs, and statins. A significant factor propelling these trials is the now-accepted total kidney volume (TKV) imaging technology by magnetic resonance imaging (MRI), which was developed through the Consortium of Radiologic Imaging Studies in Polycystic Kidney Disease Group (CRISP) that identified total polycystic kidney volume (TKV), assessed best through MRI, as tightly associated with renal dysfunction and progression of ADPKD (27,28). CRISP also demonstrated that changes in TKV can be accurately detected over a period of months, making change in TKV an acceptable marker of disease

progression in clinical trials, along with measured GFRs or serum creatinine change as principal meaningful end points.

Vasopressin V2 Receptor Antagonist Intervention

Vasopressin V2 receptor antagonists block vasopressin-mediated fluid transport into ADPKD cysts. The vasopressin V2 receptor antagonist, tolvaptan, has been evaluated in a phase 3, double-blind, placebo-controlled randomized trial over 3 years in 1445 patients with ADPKD aged 18–50 years with TKV>750 ml and estimated creatinine clearance>60 ml/min (29). The primary outcome was the annual rate of change in TKV, measured by volumetric MRI. Secondary end points included the rate of kidney function decline measured as reciprocal of serum creatinine and a composite of time to clinical progression defined as worsening kidney function, kidney pain, hypertension, and albuminuria. Over the 3-year period, the mean increase in TKV in the tolvaptan group was 2.8% per year compared with 5.5% per year in the placebo group ($P<0.001$). Analysis of secondary composite end points of time to clinical progression favored tolvaptan over placebo (44 versus 50 events per 100 follow-up years; $P=0.01$), with lower rates of worsening kidney function (2 versus 5 events per 100 person-years of follow-up; $P<0.001$) and less kidney pain (5 versus 7 events per 100 person-years of follow-up; $P=0.01$). Tolvaptan users demonstrated a slower decline in kidney function by reciprocal creatinine tracking ($P<0.001$). These are positive findings. However, tolvaptan use was associated with higher discontinuation (15.4% versus 5% with placebo) ascribed mostly to polyuria, nocturia, polydipsia, and liver toxicity, the latter prompting regulatory concern (30).

Tolvaptan remains under study in various trials in ADPKD patients for further evaluations of dose-related benefits versus adversity. On the basis of animal data and the human trial data to date, V2 antagonist intervention provides rational hope to ADPKD families and clinicians. The patient will experience a larger urine volume and must match this urine flow with sufficient daily fluid intake. Close monitoring of serum creatinine and liver functions is essential. The high monthly expense of tolvaptan may prove to be a negative factor from a cost-effectiveness perspective (31).

mTOR Pathway Inhibition

Six clinical trials evaluating mTOR inhibitors in adults with ADPKD have now been published. Five trials evaluated sirolimus (rapamycin), including the newest pilot trial by Braun *et al.* appearing in this issue of *CJASN* (32–36). One trial evaluated everolimus (37). These trials are summarized in Table 1. Patient numbers per trial varied, with follow-up ranging from 6 to 24 months. The dose of mTOR inhibitor and baseline TKV and renal function also varied across the trials (Table 1). A small benefit or no benefit in TKV change is exhibited from mTOR inhibitor use (Table 1). In the four sirolimus trials, excluding the Braun trial (32–35), the change in GFR did not reach a statistically significant difference between sirolimus versus control groups. Sirolimus associated with significant side effects in all trials, including stomatitis, acne, increased infections, increased proteinuria, and hyperlipidemia. In fact, dropout from the sirolimus group reached 29% in the Perico *et al.* trial (32–35). Walz *et al.* evaluated everolimus over 24 months in a larger number of participants across a wide range of disease stages (37). The group receiving everolimus exhibited a slower increase in TKV compared with placebo, but exhibited a greater decline in eGFR over the same time frame. Everolimus exhibited higher rates of untoward side effects and dropout reached 25% of enrollees.

Disappointment emerged from these published trials because the data did not produce evident benefit and adversity was substantial. In perspective, the trials were short, the drug dosing varied, and the stage of disease studied varied substantially. Rather than abandon mTOR therapy for ADPKD, Granthum *et al.* called for longer-duration, better structured trials (38).

It was in this context that Braun *et al.* proposed and executed a new pilot trial with 30 patients of low-dose versus standard-dose sirolimus with tracking of GFR by radiolabeled iothalamate clearance (being more precise) in addition to TKV (assessed by noncontrast computed tomography imaging) and blood levels of sirolimus (36). The investigators reasoned that radiolabeled iothalamate clearance measurements may reveal a treatment effect that might be missed by either traditional creatinine clearance or eGFR calculations from a serum creatinine measurement. They also desired precise dosing of sirolimus titrated to achieve target serum sirolimus levels. They observed that low-dose sirolimus use was associated with a significant increase in GFR measured by radiolabeled iothalamate, but concordant GFR estimated from the Chronic Kidney Disease Epidemiology Collaboration equation did not exhibit a significant increase. This discordance confirmed value in precise GFR tracking. There was no TKV change observed. Higher-dose sirolimus demonstrated no measured GFR or TKV change. These observations are meaningful in that they pave the way for the larger trial hoped for by Granthum *et al.* using radiolabeled iothalamate as the more precise GFR tracking tool (38). Shortcomings do exist in this pilot, and these are well addressed by the authors. Notwithstanding these, we should commend the effort and encourage the proposed larger trial that this pilot supports.

Somatostatin Analogs

Four published trials examine the possible benefit of regular injection of a somatostatin analog, which aims at inhibition of cAMP production in renal cells and resultant cyst development and growth (39–42). Essential data are summarized in Table 2. Three small studies focused on polycystic liver disease and assessed effect on TKV as secondary end points; their data suggested marginal benefit on TKV (39–41). A fourth randomized controlled trial evaluated 70 ADPKD patients using octreotide over 3 years (42). In this study, TKV increased less in the octreotide group compared with placebo; this difference, although persistent in direction, was no longer statistically significant at 3 years. Decline in GFR, measured by radiolabeled iothalamate clearance, was slower in the octreotide group compared with placebo, but this difference also was not statistically significant at 3 years. Octreotide associated with diarrhea and cholecystitis but showed little adversity otherwise. The researchers

Table 1. Trials evaluating mTOR inhibitors

Trial	Patients Studied (*n*)	Pharmacologic Treatment	ΔTKV (ml)	ΔGFR (ml/min)
Soliman *et al.*, 2009 (32)[a]				
Treatment	8	Sirolimus 1 mg/d×6 mo	2845±443 → 3221±311 ($P>0.05$)	32±11 → 44±19 ($P>0.05$)
Control	8		2667±399 → 3590±354 ($P<0.05$)	41±20 → 35±18 ($P>0.05$)
Perico *et al.*, 2010 (33)[b]				
Treatment	21	Sirolimus 3 mg/d×6 mo dose adjusted to serum concentration	1914±1051 → 1960±1095 ($P<0.05$)	75±23 → 73±25 ($P>0.05$)
Control	Cross-over		1907±1107 → 1977±1133 ($P=0.002$)	73±22 → 74±24 ($P\geq0.05$)
Difference			$P=0.45$	$P>0.05$
Serra *et al.*, 2010 (34)[c]				
Treatment	50	Sirolimus 2 mg/d×18 mo	907 (507–1330) → 1007 (670–1593) ($P>0.05$)	92±20 → 92±21 ($P>0.05$)
Control	50		1003 (574–1422) → 1123 (582–1731) ($P>0.05$)	91±17 → 87±20 ($P>0.05$)
Difference			$P=0.26$	$P=0.07$
Stallone *et al.*, 2012 (35)[d]				
High-dose treatment	19	Sirolimus 3 mg/d×18 mo	1493±672 → 1508±674 ($P=0.02$)	61±17 → 66±24 ($P>0.05$)
Low-dose treatment	18	Sirolimus 1 mg/d×18 mo	1712±634 → 1726±628 ($P>0.05$)	62±14 → 63±26 ($P>0.05$)
Control	18	Doses adjusted to serum concentration	1869±668 → 1905±605 ($P=0.003$)	C: 62±13 → 59±15 ($P=0.01$)
Walz *et al.*, 2010 (37)[e]				
Treatment	213	Everolimus 2.5 mg bid×24 mo	Mean ΔTKV 230 (CI, 172 to 288)	Mean ΔeGFR 8.9 ml/min
Cross-over	216		Mean ΔTKV 301 (CI, 248 to 354)	Mean ΔeGFR 7.7 ml/min
Control			$P=0.06$	$P=0.15$
Braun *et al.*, 2014 (36)				
Low-dose treatment	10	Sirolimus titrated to 2–5 ng/ml×12 mo	2479±1965 → 2115+1035 ($P>0.05$)	70±27 → 78+35 ($P<0.05$)
High-dose treatment	10	Sirolimus titrated to 5–8 ng/ml×12 mo	1718±932 → 1537±864 ($P>0.05$)	72±25 → 74±34 ($P>0.05$)
Control	10	Placebo	2072±1184 → 2059±1236 ($P>0.05$)	73±20 → 62±15 ($P<0.05$)

Data are presented as the mean±SD or median (interquartile range). CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; mTOR, mammalian target of rapamycin; TKV, total kidney volume.

[a]GFR by creatinine clearance.

[b]GFR by iohexol clearance.

[c]eGFR by CKD-EPI equation.

[d]eGFR by MDRD equation.

[e]eGFR by re-expressed MDRD equation.

Table 2. Trials evaluating somatostatin analogs

Trial	Patients Studied (*n*)	Pharmacologic Treatment	ΔTKV (ml)	ΔGFR (ml/min)
Ruggenenti *et al.*, 2005 (39)[a]				
Treatment	12	Octreotide LAR 40 mg every mo×6 mo	2551±1053 → 2622±1111 ($P<0.01$)	56±29 → 53±29 ($P>0.05$)
Control	Cross-over		2461±959 → 2623±1021 ($P<0.05$)	55±22 → 52±25 ($P>0.05$)
Hogan *et al.*, 2010 (40)[a]				
Treatment	28	Octreotide LAR 40 mg every mo×12 mo	1143±827 → 1128±796 ($P>0.05$)	68±26 → 64±25 ($P>0.05$)
Control	14		803±269 → 873±306 ($P<0.05$)	70±28 → 66±26 ($P>0.05$)
Difference			$P<0.05$	$P=0.98$
Van Keimpema *et al.*, 2009 (41)				
Treatment	27	Lantreotide 120 mg every mo×24 wk	Mean ΔTKV −17 (CI, −126 to 93)	83 (8–158) → 80 (8–153) ($P>0.05$)
Control	26		Mean ΔTKV 50 (CI −99 to 199)	91 (9–173) → 96 (−12 to 205) ($P>0.05$)[b]
Difference			$P=0.02$	
Caroli *et al.*, 2013 (42)[a,c]				
Treatment	35	Octreotide LAR 40 mg every mo×36 mo	Mean ΔTKV 220±49	88±4 → 76±4; annual ΔGFR slope over 0–3 years, −3.85 (−6.2 to −1.92)
Control	35		Mean ΔTKV 453±80	C: 77±5 → 68±6[a]; annual ΔGFR; slope over 0–3 years, −4.95 (−7.5 to −1.97)
Difference			$P=0.25$	$P=0.13$

Data are presented as the mean±SD or median (interquartile range). Octreotide LAR, octreotide acetate for injectable suspension; CI, confidence interval.
[a]GFR by iothalamate clearance.
[b]Reported as creatinine μmol/L.
[c]Slope of ΔGFR over 3 years between treatment and placebo.

expressed optimism, stating that "because of their very good risk–benefit profile, even in life-long therapy, somatostatin analogs are so far the only viable option for long-term treatment of this disorder" (42). Shortcomings included insufficient number of years of follow-up and a relatively small number of participants. Together, these four trials do not compel routine clinical use of a somatostatin analog in ADPKD, but they do provide hope and sufficient rationale for larger, longer randomized trials.

Statins

This issue of *CJASN* also includes the first published randomized placebo-controlled clinical trial of deliberate statin use to evaluate potential benefit on height-corrected TKV change of ADPKD in children and young adults (43). This trial evaluated either 20 or 40 mg pravastatin combined with an angiotensin-converting enzyme inhibitor in young patients aged 8–22 years with ADPKD. The trial enrolled 110 patients, and 91 patients completed the trial. Those patients randomized to pravastatin demonstrated significantly less increase in height-adjusted TKV over 3 years than placebo-receiving patients. There was no significant change in creatinine clearance or LDL cholesterol or proteinuria between groups. Pravastatin was well tolerated with no apparent adversity. The mechanisms of statin benefit in ADPKD are unclear. This study was well conceived, well executed, and well analyzed. Conclusions of benefit are justified. This study provides a firm foundation for careful and vigilant statin use in ADPKD, particularly if introduced early in the course of ADPKD evolution.

We are on the threshold of effective interventions for ADPKD. The novel therapies under study are reasonable and rational. Some studies were pilots. Duration varied and was largely insufficient in most trials. Stage of disease varied substantially. Power has been small. Genotype of ADPKD was not a required assessment, which may be a variable for natural progression. Thus, except for careful prescription of statins, these trials cannot compel routine use of one of these interventions outside of additional clinical trials. In my opinion, new trials should be conducted over 3–5 years and should have greater power, include biomarkers, and enroll participants of the same PKD genotype and stage of disease.

Disclosures

R.L.M. has served as a coinvestigator in the Otsuka-sponsored TEMPO trial. He does not receive and has not received compensation.

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