Autosomal Dominant Polycystic Kidney Disease (ADPKD) Clinical Trials: A Critical Appraisal

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic hereditary kidney disease in humans, occuring in 1 out of every 800–1,000 individuals, and is the cause of end-stage renal disease (ESRD) in 5–10 % of the prevalent patients on renal replacement therapy (RRT) worldwide [1]. The disease is characterized by the development, growth, and expansion of multiple renal cysts, leading to destruction of normal renal parenchyma, massively enlarged kidneys, and subsequent kidney function loss [2–4]. The natural course of ADPKD is often of progressive nature, eventually leading to ESRD in approximately 50 % of patients afflicted.

Despite extensive research over several decades, there has been no specific therapy for ADPKD that is effective in preventing or delaying disease progression. ADPKD is thus managed generically as in acquired chronic kidney disease (CKD) by treating risk factors with an emphasis on blood pressure control and treatment of its specific complications (infections, hematuria, stones, etc.) [5]. A greater understanding of the underlying complex pathogenetic mechanisms over the last decades have led to a proliferation of clinical studies investigating the potential role of emerging therapeutic strategies such as somatostatin analogues, vasopressin antagonists, mammalian target of rapamycin (mTOR) inhibitors, and statins in modulating the course of ADPKD [6].

We performed an extensive literature review of these studies using search terms: "polycystic kidney, autosomal dominant" with subheadings "diet therapy, drug therapy, mortality, prevention and control, therapy." This search yielded 392 publications. Of these, 65 studies were relevant to drug management of ADPKD, but only randomized controlled trials (RCTs) were selected for appraisal (Fig. 1.1). Each study was appraised for validity and clinical utility based on a standardized scoring system based on method of randomization, study design, sample size, end points, follow-up, bias, dropout rates, and analytical approach.

We found 22 RCTs to date (11 June 2014) on ADPKD management (Table 1.1). Most (16 of 22) of the studies were published over the current decade (2010 and onwards), six were published in the last decade (2000–2009), and only one study was conducted prior to the year 2000, and this was a subgroup analysis from the modification of diet in renal disease (MDRD) study that comprised ADPKD patients in almost a quarter of its study population.

The trials fell within six therapeutic categories:

1. Blood pressure lowering medications – 7 trials
2. Low-protein diet – 1 trial
3. Statins – 3 trials
4. mTOR inhibitors – 6 trials
5. Vasopressin receptor antagonists – 1 trial
6. Somatostatin analogues – 4 trials

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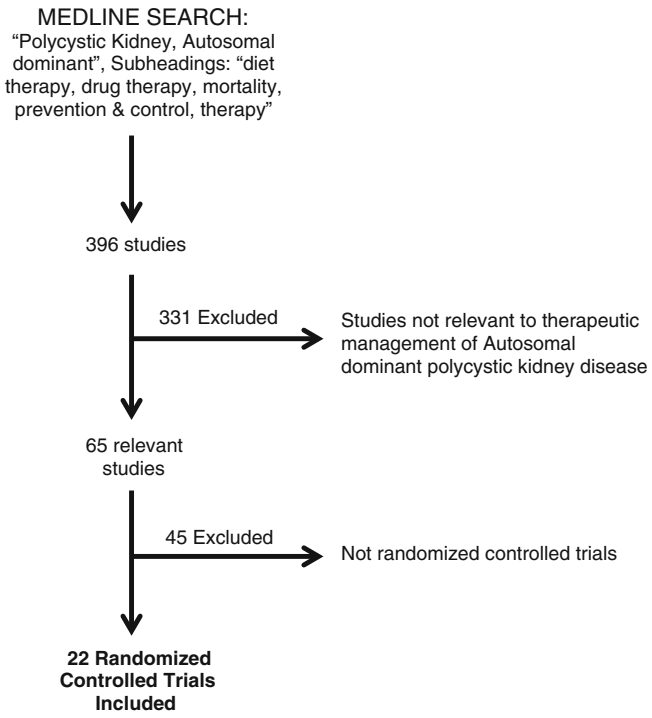

Fig. 1.1 Flow-chart summary of literature search and study selection

Five major studies out of the total 22 published clinical trials were selected for a full appraisal based on their quality and rigorous methodological framework (Table 1.1). The remaining studies, which scored relatively poorly due to their small sample sizes, inadequate follow-up, suboptimal study designs, and/or lack of rigor in conduct, were not appraised in further details (Table 1.1).

Keywords: ADPKD, Clinical trials, Management, BP, Cysts growth, Novel agents

mTOR Inhibitors Trials

The inhibition of mTOR has proved to have antiproliferative effects in a number of experimental models and clinical disease characterized by dysregulated cell growth. One of the hypotheses behind the pathogenesis of ADPKD is that a dysregulation renal tubules proliferation leads to cystic dilatations. With that notion in mind, successful attempts have been made in experimental models of PKD to slow the progression of cystic expansion as well as the associated decline in kidney function by mTOR inhibition. This has led to a number of RCTs testing this hypothesis in humans with ADPKD.

Everolimus in patients with autosomal dominant polycystic kidney disease

Walz G, Budde K, Mannaa M, et al. N Engl J Med. 2010;363(9):830–40 [7]

Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a slowly progressive hereditary disorder that usually leads to end-stage renal disease. Although the underlying gene mutations were identified several years ago, efficacious therapy to curtail cyst growth and prevent renal failure is not available. Experimental and observational studies suggest that the mammalian target of rapamycin (mTOR) pathway plays a critical role in cyst growth.

Methods: In this 2-year, double-blind trial, we randomly assigned 433 patients with ADPKD to receive either placebo or the mTOR inhibitor everolimus. The primary outcome was the change in total kidney volume, as measured on magnetic resonance imaging, at 12 and 24 months.

Results: Total kidney volume increased between baseline and 1 year by 102 ml in the everolimus group, versus 157 ml in the placebo group ($P=0.02$) and between baseline and 2 years by 230 and 301 ml, respectively ($P=0.06$). Cyst volume increased by 76 ml in the everolimus group and 98 ml in the placebo group after 1 year ($P=0.27$) and by 181 and 215 ml, respectively, after 2 years ($P=0.28$). Parenchymal volume increased by 26 ml in the everolimus group and 62 ml in the placebo group after 1 year ($P=0.003$) and by 56 and 93 ml, respectively, after 2 years ($P=0.11$). The mean decrement in the estimated glomerular filtration rate after 24 months was 8.9 ml per minute per 1.73 m^2 of body-surface area in the everolimus group versus 7.7 ml per minute in the placebo group ($P=0.15$). Drug-specific adverse events were more common in the everolimus group; the rate of infection was similar in the two groups.

Conclusions: Within the 2-year study period, as compared with placebo, everolimus slowed the increase in total kidney volume of patients with ADPKD but did not slow the progression of renal impairment.

Table 1.1 Summary of clinical appraisal scores for all the randomized controlled trials conducted in ADPKD

Trial No.	Intervention	Study with reference	Design	*N*	Intervention	Comparator	Follow-up	End points	Score %	Conclusions and comment
1	mTOR inhibitors	Stallone et al. [26]	Open label	55	Rapamycin + Ramipril	Ramipril alone	24 months	Total kidney volume, cyst volume, eGFR		Rapamycin reduced cyst volume Limited by: Open label – unblinded Short duration of follow-up Small sample size Use of surrogate end points
2	mTOR inhibitors	Soliman et al. [27]	Single blind, placebo controlled	16	Sirolimus + telmisartan	Telmisartan + placebo	24 months	Total kidney volume		Sirolimus slowed increase in total kidney volume in the first 6 months only Limited by: Lack of randomization Small sample size and inadequate power Surrogate end point
3	mTOR inhibitors	Walz et al. [7]	Double blind, placebo controlled	433	Everolimus	Placebo	24 months	Total kidney volume, cyst volume, parenchymal volume, eGFR	+13 %	*See Appraisal*
4	mTOR inhibitors	Serra et al. [11]	Open label	100	Sirolimus	No treatment	18 months	Total kidney volume, eGFR	+0 %	*See Appraisal*
5	mTOR inhibitors	Perico et al. [28]	Open label, crossover	21	Sirolimus	Conventional antihypertensives	6 months	Total kidney volume, cyst volume, eGFR		Sirolimus halted cyst growth and increased parenchymal volume Limited by: Open label and not blinded Small sample size and inadequate power Short follow-up period High dropout rates Use of surrogate end points
6	mTOR inhibitors	Braun et al. [29]	Open label	30	Rapamycin (low dose, standard dose)	Conventional anti-hypertensives	12 months	Total kidney volume, mGFR (iothalamate clearance)		Low-dose rapamycin increased mGFR Limited by: Open label and unblinded Small sample size and inadequate power Short duration of follow-up
7	Vasopression receptor antagonists	Torres et al. [13]	Double blind, placebo controlled	1,445	Tolvaptan	Placebo	36 months	Total kidney volume, eGFR	+62 %	*See Appraisal*
8	Somatostatin	Hogan et al. [30]	Double blind, placebo controlled	34	Octreotide	Placebo	12 months	Liver volume changes Total kidney volume, eGFR, quality of life		Octreotide slowed increase in total kidney volume Limited by: Study not powered to detect renal changes

(continued)

Table 1.1 (continued)

Trial No.	Intervention	Study with reference	Design	*N*	Intervention	Comparator	Follow-up	End points	Score %	Conclusions and comment
9	Somatostatin	Hogan et al. [31]	Open label	34	Octreotide	Placebo	12 months	Liver volume changes Total kidney volume, eGFR, quality of life		The previous benefit on total kidney volume was not sustained with an additional 1 year of treatment Limited by: As above, not primarily a kidney study
10	Somatostatin	Ruggenenti et al. [22]	Double blind, placebo controlled, crossover	14	Long-acting octreotide	Placebo	6 months	Total kidney volume, cyst volume, parenchymal volume, mGFR (iohexol clearance)		Octreotide slowed increase in total kidney volume and cyst volume No difference in mGFR Limited by: Very small sample size and inadequate power Follow-up period of 6 months may have been sufficient to measure health-related quality of life changes but not to detect changes in GFR
11	Somatostatin	van Keimpema et al. [32]	Double blind, placebo controlled	32	Long-acting lanreotide	Placebo	6 months	Primary end-point liver volume Total kidney volume, cyst volume, parenchymal volume, eGFR		Lanreotide slowed increase in total kidney volume Limited by: Primary end-point liver volume Study not powered to detect renal changes
12	Low-protein diet	Klahr et al. [33]	Unblinded	200	Low-protein diet	Normal protein diet	26 months	eGFR and mGFR (iothalamate)		In patients with GFR 13–24, low-protein diet slowed renal disease progression This is a subgroup analysis of the MDRD study, therefore not powered to detect changes in subgroups such as ADPKD At best hypothesis generating
13	Statin	Fassett et al. [19]	Open label	60	Pravastatin	No treatment	24 months	eGFR, urinary protein excretion		No changes with treatment Limited by: An open label trial which lends it to potential treatment bias during follow-up Small sample size and it is not clear whether the study sample had statistical power to answer the study question GFR not measured but estimated

14	Statin	van Dijk et al. [20]	Double blind, placebo controlled, crossover	10	Simvastatin	Placebo	4 weeks	iGFR (inulin clearance), effective renal plasma flow (PAH clearance)		Simvastatin increased renal plasma flow Limited by: The sample size was very small and power most likely to be inadequate This is a study primarily aimed at studying the functional and hemodynamic effects of statins in ADPKD
15	Statin	Cadnapaphornchai et al. [16]	Double blind, placebo controlled	110	Pravastatin + lisinopril	Placebo + lisinopril	36 months	HtTKV, UAE, LVMI	+73 %	*See Appraisal*
16	Anti-HTN	Nakamura et al. [34]	Unblinded	20	Telmisartan	Enalapril	12 months	BP, serum Cr, UAE		Telmisartan resulted in improved UAE Limited by: Open label trial which lends it to potential observer bias during follow-up Small sample size and it is not clear whether the sample had statistical power to answer the study question The use of surrogate end points further limits the clinical utility of the study findings; GFR not measured BP measured casually and not over 24 h; thus raising questions over accuracy of recordings
17	Anti-HTN	Ulusoy et al. [35]	Unblinded	32	Losartan	Ramipril	12 months	BP, GFR, LVMI		Both agents reduced BP and LVMI Limited by: Open label and unblended lending to observer bias Inadequate sample size to estimate impact on ADPKD progression Quality of BP measurements; BP measured casually and not over 24 h; thus raising questions over accuracy of recordings Method of CKD progression assessment; FGR not measured
18	Anti-HTN	Nutahara et al. [36]	Unblinded	49	Amlodipine	Candesartan	36 months	BP, creatinine clearance, UAE		Candesartan decreased UAE vs. amplodipine Limited by: Open label and unblinded lending to observer bias Inadequate sample size to detect changes in kidney function Quality of BP measurements; BP measured casually and not over 24 h; thus raising questions over accuracy of recordings GFR not measured

(continued)

Table 1.1 (continued)

Trial No.	Intervention	Study with reference	Design	*N*	Intervention	Comparator	Follow-up	End points	Score %	Conclusions and comment
19	Anti-HTN	Ecder et al. [37]	Unblinded	24	Enalapril	Amlodipine	60 months	Mean arterial pressure, creatinine clearance, ACR		Enalapril decreased UAE Limited by: Open label and unblinded lending to observer bias Inadequate sample size to detect changes in kidney function Quality of BP measurements; BP measured casually and not over 24 h; thus raising questions over accuracy of recordings GFR not measured
20	Anti-HTN	Zeltner et al. [38]	Double blind	46	Ramipril	Metoprolol	36 months	BP, eGFR, ACR, LVMI		No difference in outcomes between ramipril and metoprolol in ADPKD Good BP control and monitoring (24 h ABPM) in both groups Limited by: Small sample size and inadequate power to show functional differences GFR was not measured
21	Anti-HTN	Schrier et al. [25]	Unblinded	75	BP target <120/80	BP target <135–140/85–90	84 months	LVMI, eGFR		Rigorous BP control decreased LVMI Limited by: Unblinded study Small sample size and inadequate power to detect renal functional changes High dropout rates GFR not measured 24 h ABPM not recorded
22	Anti-HTN	van Dijk et al. [39]	Double blind, placebo controlled	104	Enalapril	Atenolol or placebo	36 months	mGFR (inulin)		Enalapril did not slow decline in mGFR vs. placebo or atenolol GFR measured by inulin clearance RPF measured by PAH clearance Limited by: Small sample size and inadequate power to detect renal functional changes, especially in ADPKD with normal renal function at onset 24 h ABPM not recorded

ACR urinary albumin to creatinine ratio, *ADPKD* adult polycystic kidney disease, *BP* blood pressure, *CKD* chronic kidney disease, *Cr* creatintine, *GFR* glomerular filtration rate, *eGFR* estimated GFR, *mGFR* measured GFR, *HTN* hypertension, *HtTKV* height-adjusted total kidney volume, *LVMI* left ventricular mass index, *mTOR* mammalian target of rapamycin

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **randomization** procedure well described?		−1	Randomization was only described as 1:1 with the eligible patients assigned to either receive everolimus or placebo
Double **blinded**?	+2		Described as double blinded
Is the **sample size** calculation described/ adequate?	+3		*N*=433; exceeded requirement of *N*=260 to detect a 50 % relative reduction in annual increase in total kidney volume, 90 % power and two-sided significance of 4 %. The sampling allowed for dropout and was larger than estimated SD
Does it have a hard primary **end point**?		−1	The primary outcome was a change in kidney volume measured on MRI and secondary outcomes of changes in cyst sizes and parenchymal volume at months 12 and 24 and in renal function at month 24
Is the end-point surrogate?	−2		Surrogate end points only
Is the follow-up appropriate?		−1	24-month follow-up period was likely insufficient to show any impact on disease progression towards ESRD
Was there a **Bias**?	−1		Early CKD patients only, all Caucasians and of younger age extraction
Is the dropout >25 %?	−1		~35 %: largely due to side effects associated with everolimus, including leukopenia, thrombocytopenia, and hyperlipidemia
Is the analysis **ITT**?	+3		Analysis was based on the initial treatment intent
Utility/usefulness			
Can the findings be generalized?	+1		Included patients with stage I–III CKD and ADPKD diagnosed clinically or by MRI single kidney volume >1,000 mL only
Score		13 %	**Study with major limitations**

ADPKD adult polycystic kidney disease, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *ITT* intention to treat, *MRI* magnetic resonance imaging, *SD* standard deviation

Comments and Discussion

This trial by Walz et al. was a multicenter (patients were recruited from 24 academic centers in three countries – Germany, Austria, and France), double-blinded, placebo-controlled study aimed to assess the effect of everolimus in ADPKD progression (cyst growth). It was a 2-year trial and randomized 433 patients with ADPKD. Patients were given either everolimus 2.5 mg twice a day or placebo (control). Everolimus slowed the increase in total kidney volume (TKV) but not the decline in kidney function (worsening of eGFR) compared to placebo.

Despite its robust design and large sample size, the study has important limitations on several key fronts:

1. Limited generalizability: The study was focused on patients with early CKD (Stages 1–3), a group of patients with ADPKD that hardly progress. This coupled with the use of surrogate end points and the high incidence of everolimus adverse effects, and consequent high dropout rate of 35 % limits the application of these study findings to clinical practice. Further, the study was limited to younger patients with CKD (mean age of 44 years) and all whites. The implications of the study findings in patients with a more advanced disease, the elderly, and other racial backgrounds could not be ascertained.
2. Lack of concordance of structure and function. Although, observational data in patients with ADPKD have shown that cyst volume correlates well with the disease progression [8]; Chapman et al. [8] showed TKV to be a reasonable predictor of the risk of progression to stage 3 CKD over 8-year follow-up in ADPKD. However, TKV remains a surrogate end point and its prognostic value in this study of a 2-year follow-up is uncertain.
3. Limited follow-up period: The study follow-up period of 2 years is relatively short to detect significant decline in eGFR in ADPKD which may be slowly progressive over many years especially in the initial stages of the disease.
4. Poor measures of kidney function: eGFR formulas have been shown to underestimate values and decline in measured GFR in ADPKD, suggesting that eGFR may have limited utility in ADPKD [9, 10].

Sirolimus and kidney growth in autosomal dominant polycystic kidney disease.

Serra AL, Poster D, Kistler AD, et al. N Engl J Med. 2010;363(9):820–9 [11]

Abstract

Background: In autosomal dominant polycystic kidney disease (ADPKD), aberrant activation of the mammalian target of rapamycin (mTOR) pathway is associated with progressive kidney enlargement. The drug sirolimus suppresses mTOR signaling.

Methods: In this 18-month, open-label, randomized, controlled trial, we sought to determine whether sirolimus halts the growth in kidney volume among patients with ADPKD. We randomly assigned 100 patients between the

ages of 18 and 40 years to receive either sirolimus (target dose, 2 mg daily) or standard care. All patients had an estimated creatinine clearance of at least 70 ml per minute. Serial magnetic resonance imaging was performed to measure the volume of polycystic kidneys. The primary outcome was total kidney volume at 18 months on blinded assessment. Secondary outcomes were the glomerular filtration rate and urinary albumin excretion rate at 18 months.

Results: At randomization, the median total kidney volume was 907 cm^3 (interquartile range, 577–1,330) in the sirolimus group and 1,003 cm^3 (interquartile range, 574–1,422) in the control group. The median increase over the 18-month period was 99 cm^3 (interquartile range, 43–173) in the sirolimus group and 97 cm^3 (interquartile range, 37–181) in the control group. At 18 months, the median total kidney volume in the sirolimus group was 102 % of that in the control group (95 % confidence interval, 99–105; $P=0.26$). The glomerular filtration rate did not differ significantly between the two groups; however, the urinary albumin excretion rate was higher in the sirolimus group.

Conclusion: In adults with ADPKD and early chronic kidney disease, 18 months of treatment with sirolimus did not halt polycystic kidney growth.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **randomization** procedure well described?	**+1**		Randomization list generated using a permuted block design
Double **blinded**?		**−2**	Open label, no placebo
Is the **sample size** calculation described/adequate?	**+3**		$N=100$; exceeded requirement of $N=80$ to detect a 50 % relative difference in annual increase in total kidney volume, 80 % power and two-sided alpha level of 0.05
Does it have a hard primary **end point**?		**−1**	The primary outcome was percent in change in total kidney volume. GFR and UAER at 18 months used as secondary outcomes
Is the end-point surrogate?	**−2**		Surrogate end points only
Is the follow-up appropriate?		**−1**	18-month follow-up period was likely insufficient to show effect of rapamycin on GFR; prognostic value of total kidney volume in a study of 24 year follow-up has not yet been established
Was there a **Bias**?	**−1**		Early CKD patients only, all Caucasians and of younger age extraction
Is the dropout >25 %?		**+1**	4 % (4/100 patients)
Is the analysis **ITT**?	**+3**		Described as ITT
Utility/usefulness			
Can the findings be generalized?	+1		Patients age 18–40 with ADPKD (minimum 2 % increase in total kidney volume over a 6-month pre-study period) and early CKD with GFR >70
Are the findings easily translatable?		**−1**	Clinical translatability is limited by the lack of hard non-surrogate primary end points, short follow-up time, and small sample size
Was the NNT <100?		**−1**	Negative study
Score		**0 %**	**Study with major limitations**

ADPKD adult polycystic kidney disease, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *ITT* intention to treat, *UAER* urinary albumin excretion

Comments and Discussion

This is one of the few large randomized studies on the use of mTOR inhibitors in ADPKD, and the findings are mostly in agreement with the study by Walz et al. [7]. The key objective was to determine if rapamycin (sirolimus) would slow kidney cysts growth and reduce TKV. There was no clinically meaningful reduction in TKV irrespective of patients' demographics, level of kidney function, and/or albuminuria. Though not blinded, the methodology was strong with small dropout rate (<4 %) compared to the everolimus trial [7].

The study of Serra and colleagues has a number of limitations:

1. Lack of blinding always raises concern over a potential observer bias during follow-up.
2. The follow-up period of 18 months is relatively short to detect significant clinical outcomes in ADPKD, especially early in the course of the disease.
3. The use of surrogate end points instead of hard primary end points coupled with the study being done in early CKD stages (GFR >70 ml/min), in relatively young population (18–40 years), limits the application of study results to usual clinical practice.

The above limitations make any conclusion about the impact of sirolimus on the progression of ADPKD at best hypothetical.

Vasopressin V2 Receptor Antagonists Trial

The pathogenesis of ADPKD is thought to be related to a dysregulated growth of renal tubules cells. One of the hypotheses implicates ADH (vasopressin) and the related increase in intracellular cAMP in the pathogenesis of renal cysts proliferation and luminal fluid secretion. Experimental

studies based on the suppression of vasopressin release by means of high water intake, genetic elimination of vasopressin, and vasopressin V2-receptor blockade [12] all seem to reduce the cyst burden and protect kidney function. This is the rationale behind the testing of this concept in patients with ADPKD.

TEMPO Trial

Tolvaptan in patients with autosomal dominant polycystic kidney disease.

Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS, TEMPO 3:4 Trial Investigators. N Engl J Med. 2012;367(25):2407–18 [13].

Abstract

Background: The course of autosomal dominant polycystic kidney disease (ADPKD) is often associated with pain, hypertension, and kidney failure. Preclinical studies indicated that vasopressin V(2)-receptor antagonists inhibit cyst growth and slow the decline of kidney function.

Methods: In this phase 3, multicenter, double-blind, placebo-controlled, 3-year trial, we randomly assigned 1,445 patients, 18–50 years of age, who had ADPKD with a total kidney volume of 750 ml or more and an estimated creatinine clearance of 60 ml per minute or more, in a 2:1 ratio to receive tolvaptan, a V(2)-receptor antagonist, at the highest of three twice-daily dose regimens that the patient found tolerable, or placebo. The primary outcome was the annual rate of change in the total kidney volume. Sequential secondary end points included a composite of time to clinical progression (defined as worsening kidney function, kidney pain, hypertension, and albuminuria) and rate of kidney-function decline.

Results: Over a 3-year period, the increase in total kidney volume in the tolvaptan group was 2.8 % per year (95 % confidence interval [CI], 2.5–3.1), versus 5.5 % per year in the placebo group (95 % CI, 5.1–6.0; $P<0.001$). The composite end point favored tolvaptan over placebo (44 vs. 50 events per 100 follow-up years, $P=0.01$), with lower rates of worsening kidney function (2 vs. 5 events per 100 person-years of follow-up, $P<0.001$) and kidney pain (5 vs. 7 events per 100 person-years of follow-up, $P=0.007$). Tolvaptan was associated with a slower decline in kidney function (reciprocal of the serum creatinine level, −2.61 [mg per milliliter] (−1) per year vs. −3.81 [mg per milliliter] (−1) per year; $P<0.001$). There were fewer ADPKD-related adverse events in the tolvaptan group but more events related to aquaresis (excretion of electrolyte-free water) and hepatic adverse events unrelated to ADPKD, contributing to a higher discontinuation rate (23 %, vs. 14 % in the placebo group).

Conclusions: Tolvaptan, as compared with placebo, slowed the increase in total kidney volume and the decline in kidney function over a 3-year period in patients with ADPKD but was associated with a higher discontinuation rate, owing to adverse events.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **randomization** procedure well described?		**−1**	
Double **blinded**?	**+2**		Described as double blinded
Is the **sample size** calculation described/ adequate?	**+3**		$N=1,445$; exceeded requirement of $N=600$ to detect a 20 % relative difference in total kidney volume, 85 % power and two-sided alpha level of 0.045
Does it have a hard primary **end point**?		**−1**	Change in total kidney volume, kidney function (reciprocal of serum creatinine) over 36 months
Is the end-point surrogate?	**−2**		Surrogate end points only
Is the follow-up appropriate?	**+1**		36-month follow-up period was sufficient to show effect of tolvaptan on renal function
Was there a **Bias**?		**+2**	No selection, performance, exclusion or detection biases
Is the dropout >25 %?		**+1**	20 % (288/1,445 patients)
Is the analysis **ITT**?	**+3**		Described as ITT
Utility/usefulness			
Can the findings be generalized?	**+1**		Patients age 18–50 with ADPKD (total kidney volume ≥750 mL) and early CKD with GFR >60
Was the NNT <100?		**−1**	Negative study
Score		**62 %**	

ADPKD adult polycystic kidney disease, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *ITT* intention to treat

Comments and Discussion

This study had strong methodological framework and represents the most important RCT on ADPKD to date focusing on a novel intervention. It was multicenter, double-blind, placebo-controlled, parallel-group trial of large sample size well powered to answer the study question, which was to assess efficacy and safety of tolvaptan in ADPKD. Tolvaptan slowed the increased in TKV and the decline in renal function over a 3-year period compared to placebo. It represents the only randomized control trial to date on utility of vasopressin receptor antagonists in ADPKD. It supports data from animal models of ADPKD, where vasopressin V2-receptor blockade was shown to inhibit cystogenesis [13]. Despite its strong methodological design, clinical translatability is limited due to important flaws in the study:

1. The use of changes in TKV as primary end point. While such changes may reflect subsequent or parallel changes in kidney function [8, 14], they remain surrogate to the true estimation of the decline of GFR or the incidence of ESRD. Furthermore, changes in TKV upon treatment with an agent that stimulates diuresis, and presumably the reduction of renal cysts, and kidney, urine content, cannot be equated with reduced cystogenesis.
2. Use of changes in the reciprocal of serum creatinine slope as a secondary end point for the progression of functional decline in ADPKD. Changes in serum creatinine levels, in a trial of an agent associated with changes in plasma volume due to excessive aquaresis as well as changes in fluid intake, are difficult to interpret.
3. Also the use of eGFR that seemed to agree with the changes in reciprocal of serum creatinine in this study underlies the concern about the inaccuracy of both related methods in measuring CKD progression (true/measured GFR) in ADPKD; eGFR has been shown to significantly underestimated CKD progression in ADPKD compared to measured GFR (mGFR) [9].
4. The study population included only patients with early CKD, >75 % with eGFR higher than 80 ml/min; CKD progression tends to be slow early in the course of ADPKD and accelerates considerably in later stages of renal dysfunction. Furthermore, a significant percentage of patients included in this study are likely to be non-progressive.
5. All the trial participants were required by design to increase their fluid intake in order to avoid dehydration, and it is very well known that increased water intake do suppress vasopressin-mediated cAMP generation and cystogenesis. The increased water intake on its own could have impacted on outcomes in the control group thus confounding the interpretation and possibly the power of the study.

Tolvaptan was associated with a high incidence of adverse events. This led to a high dropout rate of 20 % largely due to the side effects of tolvaptan, namely, an elevation of liver enzymes as well as aquaresis-related symptoms (thirst, polyuria). As a result of the incidence of liver injury, the US Food and Drug Administration (FDA) imposed limitations on tolvaptan use, namely, that the drug not be used in patients with underlying liver disease and that the maximal duration of tolvaptan therapy be 30 days in all other patients. This would preclude its use in a chronic condition such as ADPKD.

This study at best will be described as proof of concept indicating the potential of V2 receptor antagonism as a novel therapy in ADPKD. It is noteworthy that symptomatic pain relief was observed in patients treated with tolvaptan probably through a reduction in TKV.

Statins Trial

Statins are pleomorphic agents that have numerous cellular actions beyond the control of cellular lipids uptake and cholesterol blood levels. They have been shown to have anti-inflammatory as well as antiproliferative actions. The antiproliferative effects of statins may depend on underlying cellular transduction pathways modulation including the formation of intermediate metabolites of the mevalonate pathway, particularly the nonsterol isoprenoids, which appear to be essential in cell replication [15]. Consequently, statins have been shown to inhibit cystogenesis in experimental rodent models of ADPKD. This has been the basis of current RCTs on the impact of statins in patients with ADPKD.

Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease.

Cadnapaphornchai MA, George DM, McFann K, et al. Clin J Am Soc Nephrol. 2014;9(5):889–96 [16].

Abstract

Background and Objectives: In autosomal dominant polycystic kidney disease (ADPKD), progressive kidney cyst formation commonly leads to ESRD. Because important manifestations of ADPKD may be evident in childhood, early intervention may have the largest effect on long-term outcome. Statins are known to slow progressive nephropathy in animal models of ADPKD. This randomized double-blind placebo-controlled phase III clinical trial was conducted from 2007 to 2012 to assess the effect of pravastatin on height-corrected total kidney volume (HtTKV) and left ventricular mass index (LVMI) by magnetic resonance imaging (MRI) and urine microalbumin excretion (UAE) in children and young adults with ADPKD.

Designs, Setting, Participants, and Measurements: There were 110 pediatric participants with ADPKD and normal kidney function receiving lisinopril who were randomized to treatment with pravastatin or placebo for a 3-year period with evaluation at 0, 18, and 36 months. The primary outcome variable was a ≥20 % change in HtTKV, LVMI, or UAE over the study period.

Results: Ninety-one participants completed the 3-year study (83 %). Fewer participants receiving pravastatin achieved the primary end point compared with participants receiving placebo (69 % versus 88 %; $P=0.03$). This was due primarily to a lower proportion reaching the increase in HtTKV (46 % versus 68 %; $P=0.03$), with similar findings observed between study groups for LVMI (25 % versus 38 %; $P=0.18$) and UAE (47 % versus 39 %; $P=0.50$). The percent change in HtTKV adjusted for age, sex, and hypertension status over the 3-year period was significantly decreased with pravastatin (23 % ± 3 % versus 31 % ± 3 %; $P=0.02$).

Conclusions: Pravastatin is an effective agent to slow progression of structural kidney disease in children and young adults with ADPKD. These findings support a role for early intervention with pravastatin in this condition.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **randomization** procedure well described?		**+1**	Randomization method along with trial design given in [17]
Double **blinded**?	**+2**		Described as double blinded
Is the **sample size** calculation described/adequate?	**+3**		$N=110$; exceeded requirement of $N=100$ to detect a 30 % relative difference in the number of subjects reaching the primary end point, 80 % power and significance 0.05
Does it have a hard primary **end point**?		**−1**	Defined as ≥20 % increase in height-adjusted total kidney volume (HtTKV), left ventricular mass index (LVMI), or urinary albumin excretion (UAE)
Is the end-point surrogate?	**−2**		Surrogate end points only
Is the follow-up appropriate?	**+1**		36-month follow-up period was sufficient to show effect of statin on primary end points
Was there a **Bias**?		**+2**	There was a small randomization bias as far as the placebo group had a significantly better renal function (lower serum creatinine) at the onset
Is the dropout >25 %?		**+1**	17 % (19/110 patients)
Is the analysis **ITT**?	**+3**		
Utility/usefulness			
Can the findings be generalized?	**+1**		Pediatric patients age 8–22 with ADPKD and normal renal function receiving lisinopril as far as changes in TKV is concerned
Score		**73 %**	

ADPKD adult polycystic kidney disease, *ITT* intention to treat

Comments and Discussion

This double-blind, placebo-controlled phase III randomized controlled trial represents one of the few trials on pediatric ADPKD. The trial was based on the premise that experimental and clinical data from observational studies are suggestive of the role of statin in showing promise in some experimental models of ADPKD in rodents as well as ameliorating endothelial dysfunction and its known impact on CVD [15].

In this study, pravastatin reduced the rate of kidney enlargement, with lower progression to the end point of ≥20 % increase in height-adjusted TKV even after adjustment for age, sex, and hypertension status. Though this study represents the most robust ADPKD-specific statin trial to date, it still has notable limitations:

1. The use of surrogate renal end points (height-adjusted TKV) and microalbuminuria are not hard end points that invariably predict the incidence of ESRD in ADPKD.
2. The validity of using composite, and somewhat unrelated, end points without clear weighing has been questioned [18].
3. The study of children with ADPKD and essentially normal renal function (GFR >80 ml/min) limits the application of study results to usual clinical practice. Also, ADPKD is not invariably progressive at this stage of CKD; progression rate has not been predetermined before randomization.

Of notes previous studies of statin treatment in ADPKD were largely inconclusive due to methodological flaws [19, 20].

Somatostatin Analogue (Octerotide) Trial

A role has been postulated for GH and its second messenger insulin-like growth factor-1 (IGF-1) in the pathogenesis of ADPKD. Somatostatin has the capacity to inhibit GH release but also to inhibit adenyl cyclase and post-cAMP events that have also been implicated in cystogenesis. Preclinical animal experimentation showed a beneficial effect of somatostatin analogues in ADPKD. A number of clinical trials have since been reported.

ALADIN Study

Lancet. 2013 Nov 2;382(9903):1485–95. doi: 10.1016/S0140-6736(13)61407-5. Epub 2013 Aug 21.

Effect of long-acting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomized, placebo-controlled, multicenter trial.

Caroli A, Perico N, Perna A, Antiga L, Brambilla P, Pisani A, Visciano B, Imbriaco M, Messa P, Cerutti R, Dugo M, Cancian L, Buongiorno E, De Pascalis A, Gaspari F, Carrara F, Rubis N, Prandini S, Remuzzi A, Remuzzi G, Ruggenenti P; ALADIN study group. [21]

Abstract

Background: Autosomal dominant polycystic kidney disease slowly progresses to end-stage renal disease and has no effective therapy. A pilot study suggested that the somatostatin analogue octreotide long-acting release (LAR) could be

nephroprotective in this context. We aimed to assess the effect of 3 years of octreotide-LAR treatment on kidney and cyst growth and renal function decline in participants with this disorder.

Methods: We did an academic, multicenter, randomized, single-blind, placebo-controlled, parallel-group trial in five hospitals in Italy. Adult (>18 years) patients with estimated glomerular filtration rate (GFR) of 40 mL/min per 1.73 m(2) or higher were randomly assigned (central allocation by phone with a computerized list, 1:1 ratio, stratified by center, block size four and eight) to 3-year treatment with two 20 mg intramuscular injections of octreotide-LAR ($n=40$) or 0.9 % sodium chloride solution ($n=39$) every 28 days. Study physicians and nurses were aware of the allocated group; participants and outcome assessors were masked to allocation. The primary end point was change in total kidney volume (TKV), measured by MRI, at 1-year and 3-year follow-up. Analyses were by modified intention to treat. This study is registered with ClinicalTrials.gov, NCT00309283.

Findings: Recruitment was between April 27, 2006, and May 12, 2008. 38 patients in the octreotide-LAR group and 37 patients in the placebo group had evaluable MRI scans at 1-year follow-up; at this timepoint, mean TKV increased significantly less in the octreotide-LAR group (46.2 mL, SE 18.2) compared with the placebo group (143.7 mL, 26.0; $p=0.032$). 35 patients in each group had evaluable MRI scans at 3-year follow-up; at this timepoint, mean TKV increase in the octreotide-LAR group (220.1 mL, 49.1) was numerically smaller than in the placebo group (454.3 mL, 80.8), but the difference was not significant ($p=0.25$). 37 (92.5 %) participants in the octreotide-LAR group and 32 (82.1 %) in the placebo group had at least one adverse event ($p=0.16$). Participants with serious adverse events were similarly distributed in the two treatment groups. However, four cases of cholelithiasis or acute cholecystitis occurred in the octreotide-LAR group and were probably treatment related.

Interpretation: These findings provide the background for large randomized controlled trials to test the protective effect of somatostatin analogues against renal function loss and progression to end-stage kidney disease.

Funding: Polycystic Kidney Disease Foundation

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **randomization** procedure well described?	+1		After baseline assessment, central randomization by telephone was used to allocate study participants, in a 1:1 ratio, to 3-year octreotide LAR or placebo, according to a computer-generated randomization list
Double **blinded**?		−2	Investigators aware of allocation
Is the **sample size** calculation described/ adequate?		−3	Sample size was estimated for the main prespecified outcome variable, absolute TKV change, assuming a two group *t*-test (two sided) of the difference between octreotide LAR and placebo 40 participants were randomly assigned to octreotide LAR and 39 to placebo Sample size likely to be too small to have adequate power; see number required in TEMPO study
Does it have a hard primary **end point**?		−1	The primary end point was change in TKV, as measured by MRI, at 1-year and 3-year follow-up. Secondary end points were changes in TCV and GFR, and safety variables, including vital signs, clinical laboratory tests, and adverse events
Is the end-point surrogate?	−2		TKV as a surrogate for ADPKD progression Changes in eGFR = secondary end points, thus not powered to evaluate
Is the follow-up appropriate?	+1		1 and 3 years
Was there a **Bias**?	−2		Unblinded thus generating potential for observer bias
Is the dropout >25 %?		+1	
Is the analysis **ITT**?		−3	Not mentioned
Utility/usefulness			
Can the findings be generalized?		−1	
Was the NNT <100?			Not applicable as study negative at 3 years with no statistical difference in TKV between groups
Score	**0 %**		Inconclusive study due to the limitations highlighted above

ADPKD adult polycystic kidney disease, *TKV* total kidney volume

Comments and Discussion

The ALADIN study is at best a phase 2, proof of concept (POC), study. It is therefore hypothesis generating and not conclusive.

It has major limitations including:

1. The study is unblinded, thus subject to investigators' potential bias.
2. The study has a very small sample size unlikely to be sufficient to detect meaningful changes in TKV or renal function. 35–40 patients per group compared to the TEMPO study, with a similar primary end point of TKV measured by MRI, where 1,445 patients were randomized [13].

3. TKV has to be considered a surrogate, soft, end point, for ADPKD progression as GFR was not measured in this study. This suspicion is reinforced by the impact of the intervention at 1 year, but no longer significant statistically at 3 years. This was also supported by a study from the same group where changes in TKV and size upon treatment with octreotide were not accompanied in the short term with parallel renal functional changes (measured GFR) [22].

Conclusion

The negative ALADIN study is at best hypothesis generating, that somatostatin analogues are ineffective in ADPKD, and at worst inconclusive. Other studies on somatostatin analogues in ADPKD are mostly flawed or don't address ADPKD progression as the primary end point and are shown in Table 1.1.

General Discussion

We note that there are inherent challenges in organizing clinical trials in CKD, especially for an ADPKD-specific population. First, ADPKD is rare in adults affecting roughly 0.1 % of the population, with only 2,144 patients started on RRT annually in the United States [23]. While it may be relatively simpler to recruit large sample sizes for trials on hypertension, heart disease, or even CKD, organizing large-scale trials on an ADPKD-specific population are more challenging [4]. Also, the natural history of patients in an ADPKD cohort can vary greatly based on factors such as genotype, smoking, blood pressure control, and patient demographics. Further, ADPKD can be complicated by coexisting kidney diseases. It can be difficult to control all these factors adequately in a large-scale trial. Finally, the surrogate end points eGFR and TKV are perhaps the most commonly used end points in ADPKD studies to date. eGFR has been shown to underestimate true GFR in ADPKD [9]. Though TKV shows promise as a predictor of progression of CKD, its prognostic value in studies of limited follow-up time has not yet been explored [8]. While progression to ESRD and cardiovascular events are ideal hard end points, this may be difficult to achieve in such a rare disease with slow progression over decades. In the meanwhile, the use of surrogate end points such as changes in TKV over a long observation time requires validatory studies with measured GFR to ascertain their predictability at different stages of ADPKD. So far most published studies on the evaluation of kidney function and its progression of ADPKD have been to a large extent inconclusive due to the abovementioned limitations (Table 1.1) [5, 7, 11, 13, 16, 19, 20, 22, 24–39].

Blood pressure control remains the cornerstone in management of CKD including ADPKD. It also serves to limit the CVD complications associated with this condition. Whether intensive BP control has advantages over standard target levels is uncertain as shown by the study of Schrier and colleagues [25]. Also whether the inhibition of the renin-angiotensin-aldosterone-system (RAAS) offers therapeutic advantages over other class of antihypertensive agents is debatable [39] in spite of the hypothetical role of this system in the pathogenesis and progression of ADPKD [40]. The on-going large, double-blinded, placebo-controlled HALT-PKD trials [41] may soon provide stronger RCT evidence to define the role of RAAS inhibition in ADPKD.

Other interventions such as mTOR inhibition, somatostatin analogues, as well as statins cannot be recommended for the reasons highlighted in this review.

These should remain in the domain of clinical investigations and not be prescribed to patients with ADPKD.

Summary and Recommendations

In summary, the key issues on the interpretation and application of clinical trials in ADPKD include:

1. Lack of conformity with the standards of conducting and reporting clinical trials. Of all the 22 trials appraised, majority have not met our standard appraisal criteria and were not in conformity with the required standard of clinical trials (e.g., the CONSORT statement).
2. ADPKD being a rare disease, it is imperative to focus intervention trials on patients at higher risk of CKD progression. They warrant further identification.
3. For the reason mentioned in [4], more emphasis should be put on progressive and advanced ADPKD rather than intervening in those with ADPKD and normal renal function where the progression pattern is likely to be heterogeneous and unpredictable. Establishing those with a significant pretreatment progression rate may allow for more effective interventions and conclusive RCTs with a smaller patients' number.
4. Lack of well-validated end points and overreliance on surrogate outcomes such as total kidney volume (TKV) or cyst volume (CV) may be a major issue in ADPKD trials. The use of TKV as the gold standard for evaluation of ADPKD progression has been propelled by the development of the concept of MRI-measured TKV and its acceptability as a marker of disease progression in clinical trials, this without due consideration of significant intra- and interobserver variability of these MRI-based measurements. Also, the predictability of these measurements for the progression of ADPKD to ESRD is poorly established. Their validation need to be urgently ascertained if they are to continue to be used in drug intervention trials and not prove misleading.

5. TKV or cyst volume estimations in studies where the variability of urine output is affected by diuresis or aquaresis may confound their interpretation as the amount of residual urine within the kidneys and cysts may be a major confounder. The estimation of parenchymal kidney volume may be more helpful in such instances.
6. eGFR should not be used as it has been shown to significantly underestimate mGFR progression/decline in CKD including ADPKD.
7. Creatinine-based estimations of ADPKD progression may also be confounded by the fact that changes in tubular secretion of creatinine can be affected by interventions preserving renal tubular structure and minimizing tubular cystogenesis.

Conclusions

We are still far from the promised land of development of effective interventions for ADPKD. There is a long list of potential treatments (calcimimetics, roscovitine, triptolide, glucosylceramide inhibitors, sorafenib, thiazolidinediones, potassium channel blockers, HDAC inhibitors, and metformin [4, 42]) arising from a wealth of preclinical studies over the last several decades showing efficacy of these agents in animals. Overreliance on rodents models of PKD that may not fully be representative of human ADPKD may have encouraged misplaced enthusiasm. Clinical studies aiming to translate these findings from basic research in humans have so far been disappointing.

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