Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: https://www.tandfonline.com/loi/irnf20

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To cite this article: Rumeyza Kazancioglu & Meltem Gursu (2015) New options in the treatment of autosomal dominant polycystic kidney disease, Renal Failure, 37:4, 535-541, DOI: 10.3109/0886022X.2015.1013404

To link to this article: https://doi.org/10.3109/0886022X.2015.1013404

Published online: 16 Feb 2015.

RENAL FAILURE

http://informahealthcare.com/rnf
ISSN: 0886-022X (print), 1525-6049 (electronic)

Ren Fail, 2015; 37(4): 535–541
 DOI: 10.3109/0886022X.2015.1013404

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STATE OF THE ART REVIEWS

New options in the treatment of autosomal dominant polycystic kidney disease

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Abstract

Autosomal dominant polycystic disease (ADPKD) is one of the most common monogenic disorders, and globally is among the most common hereditary causes of end stage kidney disease. Until recently, the causes of this disease remained obscure. However, in the past decade there have been enormous advances in the understanding of the pathophysiology and genetics of this condition, and recent studies have suggested the possibility of specific treatment for slowing cyst growth. This review will focus on the new options for the control of ADPKD.

Keywords

Autosomal dominant polycystic kidney disease, treatment, mTOR inhibitors, V2 receptor inhibitors, somatostatin

History

Received 13 August 2014
Revised 21 December 2014
Accepted 4 January 2015
Published online 16 February 2015

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary disorder with a prevalence of 1 in 400 to 1 in 1000. It accounts for 5–10% of the patient population requiring maintenance dialysis in the USA and 8–10% in Europe.[1,2] Two genes, PKD1 and PKD2, have been identified to be associated with ADPKD and they are encoded as polycystin 1 and polycystin 2. Polycystins are critical for the maintenance of differentiated epithelium and are expressed in kidney, liver and pancreas tubular cells, vascular smooth muscle cells and endothelium. They have a role in multiple signaling pathways.[3] Disturbance of their function results in increased tubular cell proliferation and apoptosis, fluid secretion resulting in progressive renal cyst formation and proliferation.[4] Reduction in polycystins causes loss of polarity in tubular epithelial cells, and a secretory phenotype.[4]

Mutations of the PKD1 gene, encoding polycystin-1, a membrane receptor, account for 85% of cases. The other 15% of cases are due to mutations of the PKD2 gene, encoding polycystin-2, a calcium-permeable channel binding polycystin-1. Generally, PKD1 disease is associated with more severe clinical phenotype than PKD2, with earlier onset of end-stage kidney disease (ESRD) (mean age 54 years compared with 74 years) and more renal cysts.[4,5] In this review, current treatment options of ADPKD will be discussed.

There is at present no specific treatment for ADPKD; treatment consists of the standard therapies for chronic renal disease, including strict blood pressure control and control of hyperlipidemia.[6] There are treatment options in the pipeline targeting at attenuating the proliferation of the cysts. The major problem in the evaluation of effectiveness of therapeutic interventions in ADPKD is that the disease is a very slowly evolving condition, and glomerular filtration rate (GFR) is well maintained until relatively late in the course of the disease.[7] Thus, the use of GFR alone as a marker of disease progression over relatively short time periods is problematic, and ideally would require following patients for many years, which is generally not feasible.[6] The new surrogate marker of ADPKD progression in clinical studies has been selected as the successive evaluation of cyst size and kidney volume after the results of CRISP study.[8]

Hypertension control

Hypertension is extremely common, a significant cardiovascular risk factor and a risk factor for progression to renal failure in ADPKD. In fact we have demonstrated that hypertension was present in 72.6% of ADPKD patients in Turkey.[9] It was demonstrated that the onset of hypertension before the age of 35 years was associated with ESRD occurring 14 years earlier than in patients with the onset of hypertension after age 35 years.[10]

It is a treatable manifestation in ADPKD and may be due to a primary vasculopathy in this condition.[11] Defects in primary cilium causing endothelial dysfunction and the activation of the renin–angiotensin–aldosterone system (RAAS) are central pathophysiologic explanation for development of hypertension in ADPKD.[11] The potential benefits of giving ACE inhibitors (ACEIs) or angiotensin receptor

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blockers (ARBs) to interrupt the RAAS in polycystic disease include reduced intraglomerular pressure, reduced renal vasoconstriction, less proteinuria and decreased production of transforming growth factor beta with less fibrosis.[12] Schrier et al. reported in their epidemiological study that progression of renal disease slowed down in patients using ACEI and with lower blood pressure levels.[13]

A meta-analysis studied eight randomized controlled trials including a total of 142 subjects with ADPKD, 48% of whom were randomized to ACEI and 52% to control.[14] During a mean follow-up of 2.3 years, there was a significant decrease in protein excretion in the ACEI group, but no significant difference in disease progression as measured by change in serum creatinine. The relatively small number of patients and short period of follow-up did not allow any conclusions as to the effectiveness of ACEI in this population.[14] On the other hand, Schrier et al.[15] found that ''rigorous blood pressure control'' (goal < 120/80 mmHg) led to a greater reduction in left ventricular mass index over time than did standard blood pressure control (goal 135–140/85–90 mmHg) in ADPKD patients, and that treatment with enalapril led to a greater reduction than with amlodipine.[15] But there was no change in the progression of renal failure with lower blood pressure control and also with the use of enalapril compared to amlodipine.

The renal risks of ACEIs include ischemia from further reduction in renal blood flow (which is already compromised by expanding cysts), hyperkalemia and reversible renal failure that can typically be avoided by judicious dosing and monitoring. In addition, these drugs have the well-known side effects of cough and angioedema, and they should be avoided in pregnancy.[12]

Angiotensin-II has actions as a growth factor for epithelial cells and interstitial cells in the kidney. So it may stimulate cyst growth which in turn activates RAAS further, thus, initiating a vicious cycle. Renin production has been reported in the cyst walls in ADPKD.[16] Besides; renal chymase activity is increased in ADPKD, which in turn activates angiotensin-II through non-ACE pathway.[17] HALT-PKD trial evaluated the potential benefits of rigorous blood pressure control and inhibition of the RAAS on kidney disease progression in ADPKD based on these theories.[18]

HALT-PKD is a multicenter, randomized, double-blind, placebo-controlled trial, studying 1018 hypertensive ADPKD patients enrolled over 3 years with 4–8 years of follow-up. Primary outcomes were MR-based percent change kidney volume and a composite endpoint of time to 50% reduction of baseline estimated eGFR, ESRD or death.[18]

One arm of the study involved 558 patients with GFR values more than 60 mL/min who were randomized to either standard blood pressure group or low blood pressure group the two of each being randomized further to either lisinopril + telmisartan or lisinopril + placebo.[19] Patients in the low blood pressure group had slower increase in total kidney volume (38% vs. 44.2%) especially in younger men with larger kidneys. Patients in the low blood pressure group had greater GFR decline in the short term but similar degree of decline in GFR in long term; greater reduction in left ventricular mass and proteinuria. Patients taking lisinopril + telmisartan had lower blood pressures, lower rate of diuretic use and similar increase in total kidney volume. Decline in GFR, albuminuria, left ventricular mass, decrease in renal blood flow and increase in renal vascular resistance were similar in groups taking lisinopril + telmisartan and lisinopril + placebo.[19]

In the other arm, 486 ADPKD patients with GFR values of 25–60 mL/min were involved.[20] They were randomized to either lisinopril + telmisartan or lisinopril + placebo (blood pressure target of 120–130/70–80 mmHg).[20] Death rate, rate of ESRD, the amount of decline in GFR and hyperkalemia episodes were similar in both groups. The authors concluded that monotherapy with an ACE inhibitor is enough and addition of an ARB does not provide an additional benefit.[20]

Another challenge in antihypertensive treatment of ADPKD patients is the use of diuretics, which usually plays an important role in the antihypertensive treatment of chronic renal disease. In ADPKD, there is a concentrating defect, and these patients are often polyuric.[6] A similar concentration defect has been found in animal models of polycystic disease, and an up regulation of aquaporin 2 has been found, which is probably compensatory to the concentration defect.[21] It would seem *a priori* counter-productive to use diuretics in these patients, because of the danger of inducing hypovolemia. Ecder et al.[22] compared two groups of patients with ADPKD, one receiving antihypertensive medications including diuretics, but without ACEI, and the other receiving ACEI, but no diuretics. The follow-up period was 5.2 years. A faster loss of function occurred in the diuretic group than in the ACEI group, and it would thus seem prudent to avoid use of diuretics in this patients.[22] On the other hand, Patch et al.[23] analyzed mortality in patients with ADPKD. Patients on diuretic or RAAS blocker therapy had lower mortality compared to those receiving calcium channel blockers and beta blockers. The authors did not report any negative effect of diuretics.[23]

Treatment of hypertension effectively reduces cardiovascular mortality and may also slow down the progression of kidney disease. Based on the available data, after using diet and lifestyle modification strategies and in the absence of contraindications, an ACEI should be the initial antihypertensive agent in this population.[11] One should not forget to monitor the renal function and serum potassium levels after instituting an ACEI. The use of ACEI or ARBs in case of intolerance to ACEI is also indicated in normotensive ADPKD patients with increased left ventricular mass index or albuminuria or in those with masked hypertension.[11]

β-Blockers are also effective in reducing blood pressure in ADPKD patients. β-Blockers can be used in those patients with significant elevations in serum creatinine concentrations, concomitant cardiac disease and intolerance to both ACEI and ARBs.[11] They may be more effective than calcium-channel blockers as they also have mild RAAS-inhibitory properties.

Calcium-channel blockers should be added for control of hypertension after using ACEI, ARBs and β-blockers. Diuretics should only be considered in conjunction with inhibitors of the RAAS and under careful monitoring of serum creatinine, particularly in patients with advanced renal failure where the risk of acute deterioration of kidney function on the combination therapy with a diuretic is higher.[11] Based on currently available evidence, the blood pressure goal is

<130/80 mmHg for hypertensive ADPKD patients with or without left ventricular hypertrophy.

Statin use

Dyslipidemia is common in chronic renal disease, and is a risk factor for progression.[6] HMG-CoA reductase inhibitors (statins) appear to have pleiotropic effects, including inhibition of proliferation of a number of kidney cell lines, induction of apoptosis, inhibition of chemokine and cytokine release by mesangial cells and monocytes, and inhibition of matrix components by mesangial cells.[6] Lovastatin has been shown in heterozygous male Han:SPRD rats to reduce the severity of cystic disease as assessed by kidney size, volume density of cysts and serum urea nitrogen concentration.[24] The short-term effects of statins in 10 normo-cholesterolemic normotensive ADPKD patients were studied by van Dijk et al.[25] in a double-blind cross-over study over a four week period. Simvastatin caused an increase in GFR and effective renal plasma flow, and at the same time significantly enhanced vasodilator response to acetylcholine in the forearm.[25] It is believed that these renoprotective effects are mediated by statin-related inhibition of G-proteins with resultant decreased cell proliferation.[26] The randomized double-blind placebo-controlled trial conducted with 110 children with ADPKD and normal kidney function studied the effect of pravastatin on the progression of disease.[27] All patients had lisinopril treatment. They were randomized to treatment with pravastatin or placebo. The primary outcomes were ≥20% change in TKV, LVMI or albuminuria over three years. The number of patients reaching end point for TKV was significantly lower in the pravastatin group.[27]

Water treatment

Both *in vivo* and *in vitro* studies demonstrated that cAMP promotes cellular proliferation and transepithelial fluid secretion leading to cyst formation and expansion.[28] Vasopressin (AVP) enhances cyst growth by increasing the cAMP levels in the epithelial cells of the cysts. Thus, the reduction of plasma AVP levels by increasing the water intake has been tested. Nagao et al.[29] tested the effect of increased water intake sufficient to lower Uosm in rats with the homolog of autosomal recessive PKD. The resultant polyuria and Uosm below that of plasma were associated with a reduction in renal volume, reduced renal cyst area and a decrease in the blood urea nitrogen levels below the controls, consistent with a positive therapeutic effect.[29] Barash et al.[30] compared ADPKD patients with control subjects for urine cAMP levels and urine osmolality after acute and sustained water load. Both urine cAMP level and osmolality decreased in both groups after acute water lading. The decrease in daily urine cAMP excretion in patients with ADPKD was not significant with chronic water loading in spite of significant increase in urine volume and decrease in urine osmolality.[30] The authors concluded that urine cAMP excretion may be used to monitor response to sustained water loading in ADPKD. But there is need for further studies to show the effect of water loading on end points like GFR and kidney volume.[30]

Higashihara et al.[31] studied the effect of increased water intake in 35ADPKD patients with GFR level more than 50 mL/min. Patients were free to be involved either in the high water intake group (50 mL/kg/day) or free water intake group. The increase in TKV was slightly more in the high water intake group, although the difference was not statistically significant. The decrease in eGFR was also similar in both groups.[31] But the low number patients and lack of a true randomization were the major limitations of this study. So, it is difficult to comment strictly on this issue with that study also.[31]

Torres et al.[32] attempted to define a safe upper limit that is experience based in ADPKD patients and 3–4 L of water daily was advised to be prescribed for individuals with ADPKD at stage 4 CKD or better. Caffeinated beverages should be discouraged because caffeine inhibits phosphodiesterase; enhances cAMP accumulation and potentiates the effects of AVP on chloride secretion, cell proliferation and cyst growth, at least *in vitro*.[33] Calorically sweetened beverages and fruit drinks are major contributors to the epidemic of obesity worldwide, hence should be avoided.[34] Because drinking tap water has been associated in some studies with a slightly increased risk for bladder cancer in men, whereas non-tap water has not, high-quality or bottled water may be preferable.[34]

EGFR tyrosine kinase inhibitors

The epidermal growth factor (EGF)/transforming growth factor-alpha (TGF-alpha)/EGF receptor (EGFR) axis is important in promoting tubular epithelial cell proliferation and cyst formation in ADPKD.[6] EGFR expression is increased in cystic renal and hepatobiliary epithelia.[6] EGFR tyrosine kinase inhibitors have been successful in inhibiting the disease process in bpk mice and in the Han:SPRD rats.[35] However, in PCK rats, a model of human ADPKD, EGFR tyrosine kinase inhibitors failed to affect the disease.[6] At present, the role of EGF in ADPKD is unclear.

mTOR inhibitors

In ADPKD, polycystin deficiency permits excessive kinase activity in the mTOR pathway and hence the development of renal cysts.[12] It is known that the mTOR system can be blocked by rapamycin. Rapamycin is a macrocyclic lactone that is derived from *Streptomyces hygroscopicus* and exerts antiproliferative and growth-inhibiting effects as well as antifibrotic effect by inhibition of the mTOR enzyme.[36] It has been used in kidney transplant recipients as a part of maintenance immunosuppressive therapy and as an antitumor agent as well as in drug-eluting stents to prevent coronary artery stenosis.[36]

Wahl et al.[37] found that inhibition of mTOR with rapamycin slows PKD progression in rats. Tao et al.[38] showed that sirolimus markedly slowed disease progression in Han:SPRD (cy) rats, in terms of decreased proliferation in cystic and non-cystic tubules, inhibition of renal enlargement and cystogenesis, and prevented loss of renal function.

Shillingford et al.[39] reported in their study that mTOR is inappropriately active in ADPKD, rapamycin may avert this pathway.

Because excessive proliferation of the biliary epithelium is a prominent feature of the polycystic liver that accompanies ADPKD, rapamycin was tested in these patients.[40] The volumes of polycystic livers and kidneys in renal transplant ADPKD patients were documented among those who had participated in a prospective randomized trial that compared a sirolimus (rapamycin)-containing immunosuppression regimen to a tacrolimus-containing regimen.[40] Treatment with the sirolimus regimen for an average of 19.4 months was associated with an $11.9 \pm 0.03\%$ reduction in polycystic liver volume, whereas treatment with tacrolimus for a comparable duration was associated with a $14.1 \pm 0.09\%$ increase. A trend toward a greater reduction in native kidney volume was also noted in the sirolimus group compared with the non-sirolimus group.[40] In summary, treatment with sirolimus was associated with decreased polycystic liver volume, perhaps by preventing aberrant activation of mTOR in epithelial cells lining the cysts.[40]

To assess the effects of mTOR inhibition on ADPKD progression, a randomized study (The SIRENA Study) comparing a 6-month treatment with sirolimus or conventional therapy alone on the growth of kidney volume and its compartments in 21 ADPKD patients with a GFR >40 mL/min was conducted.[36] Compared to the baseline, post-treatment mean total kidney volume increased less on sirolimus (46 ± 81 mL) than on conventional therapy (70 ± 72 mL). Cyst volume was stable on sirolimus and increased by 55 ± 75 mL on conventional therapy, whereas parenchymal volume increased by 26 ± 30 mL on sirolimus and was stable on conventional therapy.[36] Sirolimus had no appreciable effects on intermediate volume and GFR. Albuminuria and proteinuria significantly increased during sirolimus treatment.[36] In summary, it was demonstrated that sirolimus halted cyst growth and increased parenchymal volume in ADPKD patients.

SUISSE ADPKD study was an 18-month, open-label, randomized and controlled trial that investigated whether sirolimus halted the growth in kidney volume among ADPKD patients.[41] One hundred patients between the ages of 18 and 40 years were randomly assigned to receive either sirolimus (target dose, 2 mg daily) or standard care. All patients had an estimated creatinine clearance of at least 70 mL/min. Serial magnetic resonance imaging was performed to measure the volume of the polycystic kidneys.[41] The median increase in kidney volume over the 18-month period was similar in the groups, 99 cm^3 in the sirolimus group and 97 cm^3 in the control group. The GFR did not differ significantly between the two groups; however, the urinary albumin excretion rate was higher in the sirolimus group.[41] Thus, it was concluded that in adults with ADPKD and early chronic kidney disease, 18 months of treatment with sirolimus did not halt polycystic kidney growth.[41]

Walz et al.[42] randomly assigned 433 ADPKD patients 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. 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.[42]

In a more recent study (RAPYD-Study) the role of rapamycin in the reduction of the progressive increase in single cyst and total kidney volume in type I ADPKD was assessed.[43] Moreover, the decline in renal function and the optimal rapamycin dose was determined. Fifty-five patients with type I ADPKD were enrolled and randomized to receive ramipril (Group A), ramipril + high-dose rapamycin (Group B, trough level 6–8 ng/mL) and ramipril + low-dose rapamycin (Group C, trough levels 2–4 ng/mL).[43] Single cyst final volume was not significantly different in the three groups, although it was increased in Group A compared with the baseline, whereas in Groups B and C, it was significantly reduced. No difference in renal function at 24 months was observed among the study groups. This study suggested that rapamycin does not influence the progression of type I ADPKD, although the higher drug dose tested prevented both the increase in kidney volume and the worsening of renal function.[43]

Rapamycin has significant side effects such as hypertriglyceridemia, hypercholesterolemia, thrombocytopenia, anemia, leukopenia, oral ulcers, impaired wound healing, proteinuria, thrombotic thrombocytopenic purpura, interstitial pneumonia, infection and venous thrombosis.[12] Many of these appear to be dose-related and can generally be reversed by stopping or reducing the dose. Currently this drug is not approved by the US Food and Drug Administration for the treatment of ADPKD.[12]

Somatostatin analogs

In a study, Ruggenenti et al.[44] performed a randomized cross-over trial of somatostatin in 12 ADPKD patients over a period of 6 months. The rationale for this study was the clinical observation of prevention of disease progression over a period of 2 years in a woman receiving octreotide for other reasons. Progression of disease was measured as increase in kidney volume by CT. They demonstrated that somatostatin significantly slowed kidney volume increase.[44]

Caroli et al.[45] aimed to assess the effect of 3 years of octreotide-LAR treatment on kidney and cyst growth and renal function decline in ADPKD patients. Adult patients with estimated GFR of >40 mL/min were randomly assigned to three year treatment with two 20 mg intramuscular injections of octreotide-LAR ($n = 40$) or 0.9% sodium chloride solution ($n = 39$) every 28 days. The primary endpoint was change in total kidney volume.[45] Though at one year follow-up, mean total kidney volume increased significantly less in the octreotide-LAR group compared with the placebo group; at the three year follow-up, mean total kidney volume increase in the octreotide-LAR group was not different than the placebo group.[45]

The currently ongoing DIPAK study is a randomized, controlled trial in which subcutaneous lanreotide is planned to be compared with standard care for 120 weeks regarding the slope of eGFR (primary outcome), change in eGFR level, change in kidney and liver volume measured with magnetic

resonance imaging and change in quality of life (secondary outcome measures).[46]

V2 receptor inhibitors

The major advances in knowledge of the pathophysiology of cyst formation have indicated that cAMP plays a central role in the proliferation and secretion of cyst cells.[6] Thus inhibition of cAMP production would be a direct, physiological approach to reducing cyst expansion. Since AVP is the main stimulator of adenylyl cyclase, and cAMP production in these cells, blockade of AVP using V2 receptor (VPV2R) antagonists could be therapeutic in polycystic disease.[6] This has been first tested using a non-peptide AVP antagonist (OPC-31260), which is 82 times more selective to rat V2 receptors than to rat V1a receptors.[6] Torres et al.[47] used the Pkd-/WS25 mouse, mouse model of human ADPKD (PKD2) that reliably develops cysts after 3 months. OPC-31260 administered in the diet to these mice between 3 and 16 weeks of age markedly reduced renal cAMP production and inhibited disease development, as indicated by lower kidney weights, plasma BUN concentrations, renal cyst volumes, mitotic and apoptosis indices.[47] Similar results were obtained in rat models of autosomal recessive PKD and nephronothisis.[6]

In TEMPO 3–4 1445 patients, 18–50 years of age, who had ADPKD with a total kidney volume of 750 mL or more and an estimated glomerular filtration rate of >60 mL/min, were randomly assigned to receive tolvaptan, a V_2-receptor antagonist, at the highest of three twice-daily dose regimens that the patient found tolerable, or placebo.[48] The primary outcome of this study was the annual rate of change in the total kidney volume. The secondary end points included a composite of time to clinical progression and rate of kidney-function decline. During the following three years, the increase in total kidney volume in the tolvaptan group was 2.8% per year versus 5.5% per year in the placebo group.[48] Hence the composite end point favored tolvaptan over placebo with lower rates of worsening kidney function and kidney pain.[48] 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 including aquaresis and hepatic adverse events unrelated to ADPKD.[48]

Recently Myint et al.[49] performed a meta-analysis of randomized trials of interventions that have been hypothesized to reduce the progression of total kidney volume and renal function in ADPKD. Eleven trials (2262 patients) were included. Compared to placebo, Target of Rapamycin complex 1 (TORC1) inhibitors (five trials, $n = 619$), showed no significant change in total kidney volume, total cyst volume or eGFR. Somatostatin analogues (three trials, $n = 157$) reduced TKV by 9% (CI: −10.33% to −7.58%) but did not alter eGFR. The AVP receptor antagonist ($n = 1455$) attenuated total kidney volume increase to 3%/year and slowed kidney function decline over a 3-year period. A single trial ($n = 41$) of eicosapentaenoic acid did not alter the progression of either total kidney volume or renal dysfunction.[49] Adverse events were significant for interventions in all trials compared to placebo. These data suggested that somatostatin analogues and AVP receptor antagonists attenuate total kidney volume increase.[49]

Novel therapies

Bosutinib (SKI-606)

It was found in animal studies that increased Src activity correlates with disease progression in ARPKD and pharmacologic inhibition of its activity with SKI-606 ameliorates the renal and biliary lesions. So, bosutinib may be a promising agent for the treatment of ADPKD in the future.[50]

Triptolide

Triptolide is a natural compound derived from the traditional Chinese medicine Lei Gong Teng. It has been shown to restore cytosolic Ca^{2+} release and lead to growth arrest in $Pkd1^{-/-}$ murine kidney epithelial cells.[51] It has been reported to have moderate effects on reducing cyst formation in $Pkd1^{-/-}$ mice.[52] These studies suggest triptolide could be a potential treatment for ADPKD. A phase-2 trial of triptolide for ADPKD is currently ongoing in China.

Sorafenib

It was reported that sorafenib blocks cAMP dependent proliferation of cultured cyst epithelial cells.[53]

R-Roscovitine

Pharmacological inhibition of cell cycle progression with the cyclin-dependent kinase (CDK) inhibitor R-roscovitine was shown in animal models to suppress kidney cystic disease progression as well as liver cystogenesis by way of effective inhibition of cell cycle, proliferation and apoptosis.[54]

Histone deacetylases (HDAC) inhibitors

HDACs regulate cellular functions either through deacetylation of histones or nonhistone transcription factors, regulate specific cellular processes. HDAC inhibitor TSA-treated Pkd1 mutant Mouse embryonic kidney cells were found to be proliferated ~60% slower than nontreated.[55] So, HDAC inhibitors are potential therapeutic agents for the treatment of ADPKD.

The cystic fibrosis transmembrane conductance regulator (CFTR) inhibitors

CFTR protein is a cAMP-regulated Cl^- channel that facilitates epithelial fluid secretion. CFTR is required for cyst expansion in autosomal dominant polycystic kidney disease. So, CFTR may be a treatment target in ADPKD.[56]

KCa3.1 potassium channel blockers

KCa3.1 channels are essential for transcellular chloride secretion and net fluid transport into the kidney cysts by maintaining the electrochemical driving force for chloride efflux through apical chloride channels. Pharmacological inhibitors of KCa3.1 channels may delay the progression of kidney failure.[57]

In conclusion, the patient with ADPKD can present many therapeutic challenges. Control of blood pressure has prime importance for both renal survival and for decreasing cardiovascular morbidity and mortality. ACEI are the mainstay of treatment of hypertension followed by beta blockers and calcium channel blockers, in order. Diuretics should be used cautiously when necessary. Statins have been shown in some studies to improve renal functions. The amount of water that the patients should drink has not been clearly defined; but 3–4 L/day seems to be the optimal amount according to the studies that have been conducted up to now. Caffeinated beverages should be discouraged. There are conflicting results about the use of sirolimus to halt cyst growth and this drug is not approved by the US Food and Drug Administration for the treatment of ADPKD. Somatostatin analogues and AVP receptor antagonists attenuate total kidney volume increase but are associated with adverse event that render their use difficult. There are many novel drugs that are being studied in patient with ADPKD. These new treatment approaches combined with established ones should begin to have a favorable impact on outcomes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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