Journal of Nephrology
https://doi.org/10.1007/s40620-021-01062-6

REVIEW

Therapeutic advances in ADPKD: the future awaits

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Received: 13 January 2021 / Accepted: 4 May 2021

Abstract
Autosomal dominant polycystic kidney disease (ADPKD) is a heterogeneous genetic disorder included in ciliopathies, representing the fourth cause of end stage renal disease (ESRD), with an estimated prevalence between 1:1000 and 1:2500. It is mainly caused by mutations in the PKD1 and PKD2 genes encoding for polycystin 1 (PC1) and polycystin 2 (PC2), which regulate differentiation, proliferation, survival, apoptosis, and autophagy. The advances in the knowledge of multiple molecular pathways involved in the pathophysiology of ADPKD led to the development of several treatments which are currently under investigation. Recently, the widespread approval of tolvaptan and, in Italy, of long-acting release octreotide (octreotide-LAR), represents but the beginning of the new therapeutic management of ADPKD patients. Encouraging results are expected from ongoing randomized controlled trials (RCTs), which are investigating not only drugs acting on the calcium/cyclic adenosin monoposphate (cAMP) pathway, the most studied target so far, but also molecules targeting specific pathophysiological pathways (e.g. epidermal growth factor (EGF) receptor, AMP-activated protein kinase (AMPK) and KEAP1-Nrf2) and sphingolipids. Moreover, studies on animal models and cultured cells have also provided further promising therapeutic strategies based on the role of intracellular calcium, cell cycle regulation, MAPK pathway, epigenetic DNA, interstitial inflammation, and cell therapy. Thus, in a near future, tailored therapy could be the key to changing the natural history of ADPKD thanks to the vigorous efforts that are being made to implement clinical and preclinical studies in this field. Our review aimed to summarize the spectrum of drugs that are available in the clinical practice and the most promising molecules undergoing clinical, animal, and cultured cell studies.

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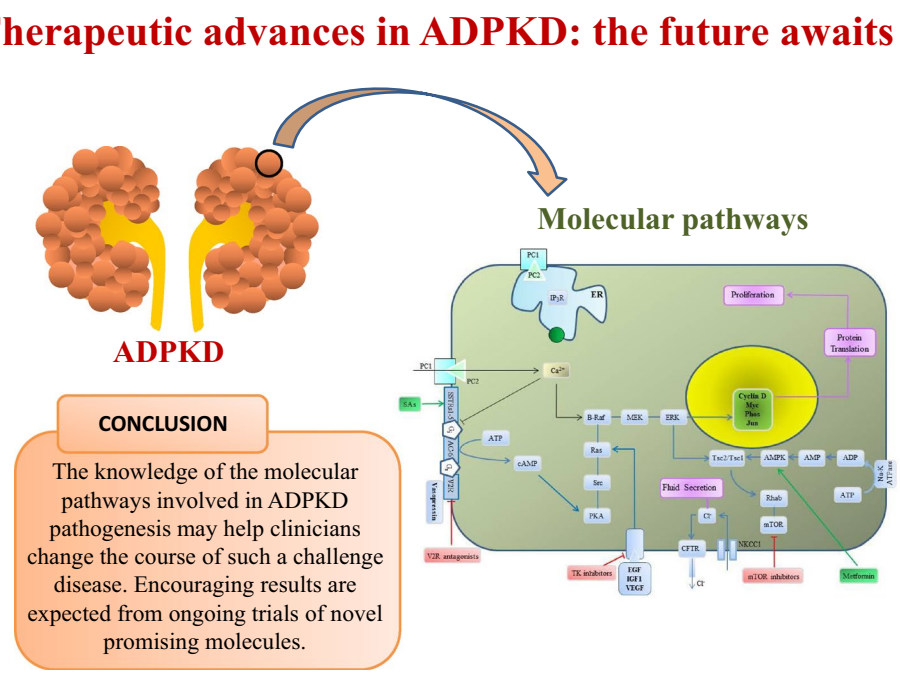
Published online: 19 May 2021

Graphical abstract



Keywords Autosomal dominant polycystic kidney disease · Total kidney volume · Glomerular filtration rate · Molecular pathway · Targeted therapy

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a heterogeneous genetic disorder included in ciliopathies, representing the fourth cause of end stage renal disease (ESRD), with an estimated prevalence between 1:1000 and 1:2500. ADPKD is mainly caused by mutations in the PKD1 and PKD2 genes encoding for polycystin 1 (PC1) and polycystin 2 (PC2), both of which are expressed on the primary cilium [1]. PCs regulate differentiation, proliferation, survival, apoptosis, and autophagy [2]. Calcium/cyclic adenosin monoposphate (cAMP) signalling plays a central role in ADPKD pathophysiology; its upregulation causes Protein Kinase A (PKA) activation, promoting cystogenesis and chloride and fluid secretion through cystic fibrosis transmembrane conductance regulator (CFTR) [3]. cAMP and PKA are also responsible for mitogen activated protein kinase (MAPK) cascade and mammalian Target Of Rapamycin (mTOR) activation [4, 5], Wnt-dependent tubulogenesis [6], increase in ciliary length [7], and centrosomal amplification [8]. Though cAMP signalling is the most studied pathway, many other transduction mechanisms are modulated by PCs [9–11]. Moreover, cyst growth triggers immune system response which determines interstitial inflammation and fibrosis, causing progressive renal function decline. Pharmacological therapies reducing cAMP production (i.e. tolvaptan and octreotide), along with supportive measures (i.e. blood pressure control, increased fluid intake, sodium chloride intake reduction and smoking cessation) are the mainstays of current management of the disease.

Deeper knowledge of the pathogenic pathways involved in ADPKD led to the development of several treatments which are currently under investigation (Figs. 1, 2).

Current therapies

Tolvaptan

Tolvaptan is a vasopressin-2-receptor antagonist reducing cAMP levels [12, 13] in collecting ducts, connecting tubules and thick ascending limbs of Henle [14], which are sites of cystogenesis. It was originally approved in Japan in March 2014 and in Canada in February 2015. On May 27th, 2015, it received its first market authorization from the European Medicines Agency in order to slow cysts and renal insufficiency progression in ADPKD patients aged 18–50 with Chronic Kidney Disease (CKD) stage 1–3, and rapid progression of the disease. In August 2018 its use was extended to individuals with stage 4 CKD. On April 24,

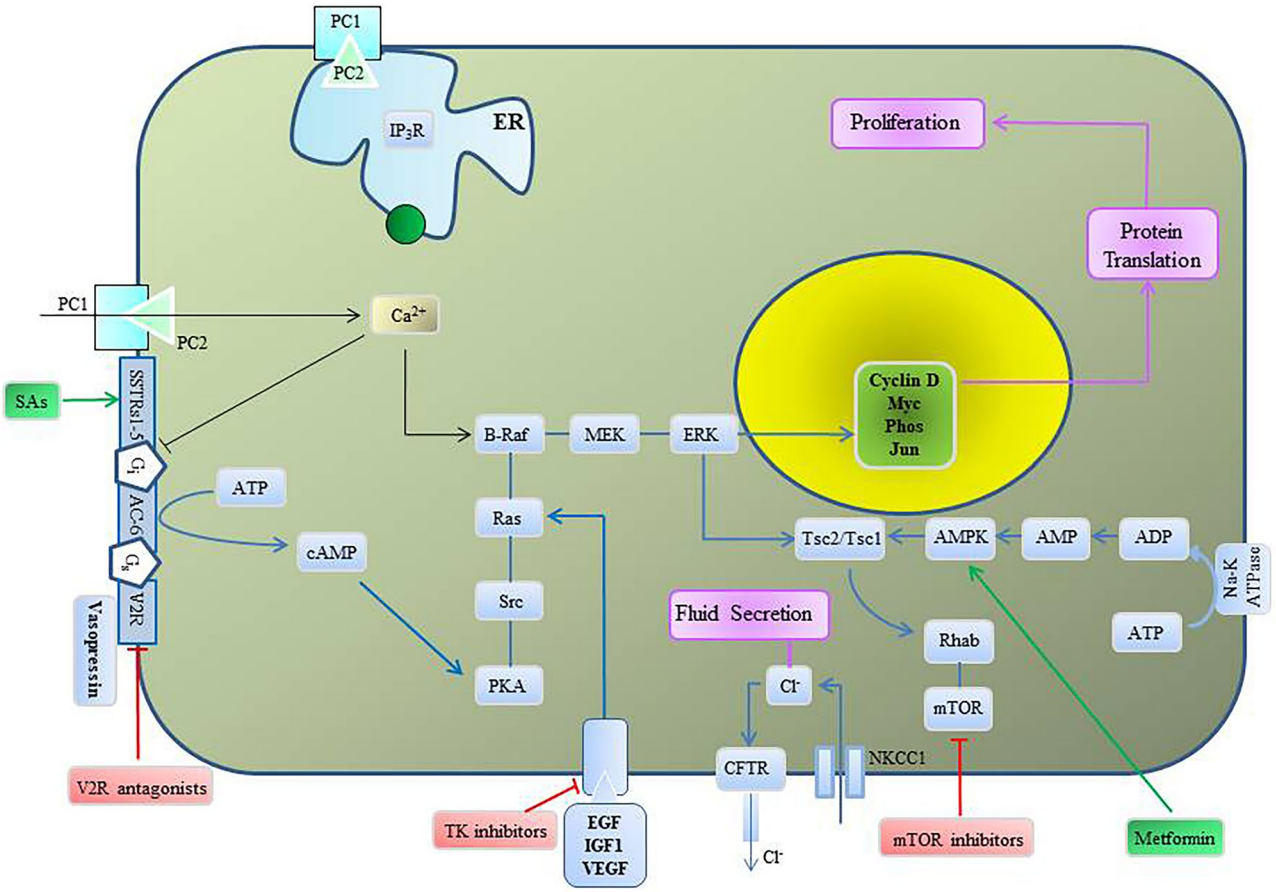


Fig. 1 Therapeutic targets studied in clinical trials. *PC* polycystin, *AMPK* adenosine monophosphate-activated protein kinase, *cAMP* cyclic adenosine monophosphate, *EGF* epidermal growth factor, *SAs* somatostatin analogues, *SSTR* somatostatin receptors, *V2R* vasopressin 2 receptor, *V2R ant* vasopressin 2 receptor antagonists, *EGF* epidermal growth factor, *IGF* insulin growth factor, *VEGF* vascular endothelial growth factor, *TK inhibitors* tyrosine kinase inhibitors, *mTOR inhibitors* mammalian target of rapamycin inhibitors. Inhibitor drugs are represented in red; activator drugs are represented in green.

2018, tolvaptan was approved by the Food and Drug Administration as the first treatment in the United States for adult patients with ADPKD.

The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 study showed a total kidney volume (TKV) reduction of 45% and an estimated Glomerular Filtration Rate (eGFR) decline of 26% in early (i.e. Cockcroft and Gault eGFR higher than 60 mL/min) but rapidly progressive ADPKD patients treated with tolvaptan vs placebo over 3 years. The most important adverse effect was hepatotoxicity, apparently dose-unrelated and completely resolving upon tolvaptan discontinuation [15]. Aquaretic symptoms (polyuria, pollakiuria, nocturia, thirst, polydipsia) resulted in treatment discontinuation in up to 10% of patients treated with tolvaptan, most of whom were young males with better kidney function and higher urine osmolarity [16]. In the extension study, TEMPO 4:4, a significant eGFR difference between the two groups was maintained, especially in patients with more severe disease [17]. However, the "early treated" patients (i.e. patients who successfully completed TEMPO 3:4) showed a non-significant TKV change compared to the "delayed treated" patients (i.e. patients who received placebo in TEMPO 3:4 and tolvaptan in the two-year follow-up period of TEMPO 4:4). This result suggests that tolvaptan exerts its maximum effect in the first two years of treatment. In the Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial, which also included more advanced CKD stages, tolvaptan slowed eGFR decline compared to placebo at 1-year follow-up, especially in CKD stage 2–3a, albeit with no significant benefits in patients older than 55 [18] (Table 1).

TKV has been accepted by the Food and Drug Administration and European Medicines Agency as a prognostic biomarker for patients at high-risk for progression [19] and its importance was confirmed by the Mayo Clinic which developed a validated TKV-based risk assessment tool to

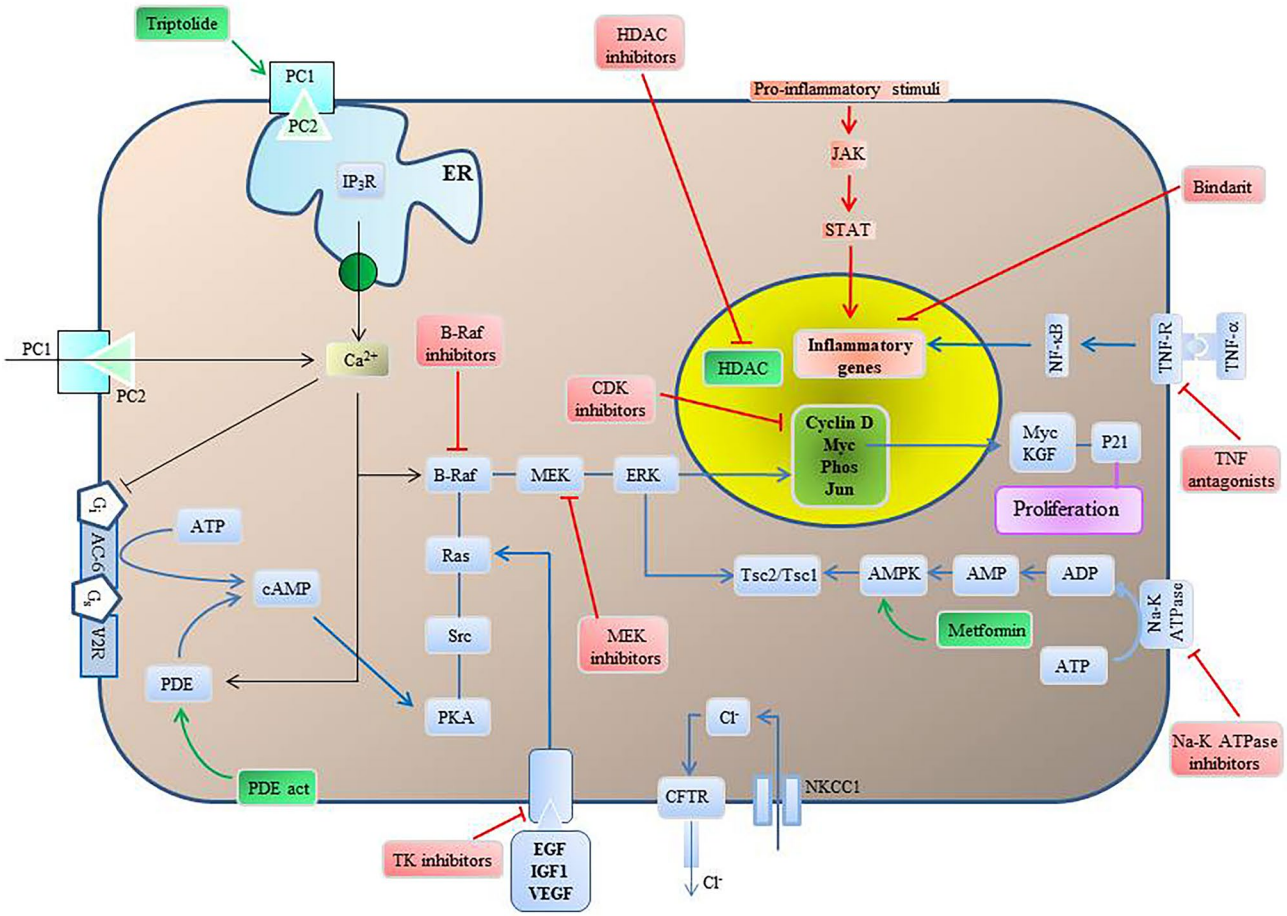


Fig. 2 Therapeutic targets studied in animals and cultured cells. *PC* polycystin, *AMPK* adenosine monophosphate-activated protein kinase, *cAMP* cyclic adenosine monophosphate, *EGF* epidermal growth factor, *PDE act* phosphodiesterase activators, *MAPK* mitogen-activated protein kinase, *V2R* vasopressin 2 receptor, *V2R ant* vasopressin 2 receptor antagonists, *EGF* epidermal growth factor, *IGF* insulin growth factor, *VEGF* vascular endothelial growth factor, *TK inhibitors* tyrosine kinase inhibitors, *TNF antagonists* tumor necrosis factor-alfa antagonists, *CDK inh* cyclin-dependent kinase inhibitors, *HDAC inhibitors* histone deacetylase inhibitors. Inhibitor drugs are represented in red; activator drugs are represented in green.

identify "high-risk" patients, using age and height-adjusted TKV. Moreover, with the approval in multiple countries of tolvaptan for the treatment of "high-risk" patients with ADPKD, TKV-based risk assessment takes on a crucial role in the clinical setting in order to identify patients who can get access to this therapy [20]. Magnetic resonance imaging or computed tomography images by manual segmentation are currently considered the "gold standard" for TKV measurement; however, this method is burdensome and requires high radiologic expertise. On the other hand, new radiologic approaches are under investigation to streamline the determination of TKV, which can be derived through an ellipsoid formula with the measurement of only three axes for each kidney [21] or by an automatic localization model of ADPKD using Artificial Intelligence [22].

Somatostatin analogues

Somatostatin analogues, including octreotide, lanreotide and pasireotide lower cAMP levels through their interaction with G-protein coupled somatostatin receptors.

On August 3rd, 2018, long-acting release octreotide (octreotide-LAR) was approved in Italy alone for the treatment of ADPKD adult patients with eGFR ranging from 15 to 30 mL/min/1.73 m^2 at high risk of progression towards ESRD.

The Long-Acting somatostatin on DIsease progression in Nephropathy due to autosomal dominant polycystic kidney disease (ALADIN 1) trial, conducted in patients with eGFR Modification of Diet in Renal Disease (MDRD) ≥ 40 mL/min/1.73 m^2, showed that the annual slope of TKV increase was significantly lower in the octreotide group compared to placebo. However, the difference in TKV increase at the end

Table 1 Clinical trials targeting cAMP, EGFr, AMPK pathways, metabolism and diet, KEAP1-Nrf2 pathway, sphingolipids

Clinical trials	Agent	Mechanism	Key inclusion criteria	Primary outcome/ results	Secondary outcome/ results	Phase	Estimated study completion date
Targeting cAMP pathway							
TEMPO 3:4 [15] (2012)	Tolvaptan	V2R antagonist	Age 18–50, eCrCl ≥ 60, TKV ≥ 750 mL	TKV growth reduction by 49% per year in tolvaptan vs placebo group ($p < 0.001$)	Lower rates of worsening kidney function ($p < 0.001$), kidney pain ($p = 0.007$); eGFR loss reduction by 26% per year ($p < 0.001$) in tolvaptan vs placebo group	3	Completed and published
TEMPO 4:4 [17] (2018)	Tolvaptan	V2R antagonist	Pts from TEMPO 3:4, early (already in tolvaptan) and delayed treated (ex placebo)	No sustained treatment difference on TKV in tolvaptan vs placebo group ($p = 0.38$)	Sustained effect on eGFR in tolvaptan vs placebo group ($p < 0.001$)	4	Completed and published
REPRISE [18] (2017)	Tolvaptan	V2R antagonist	Age 18–55, eGFR 25–65 or Age 56–65, eGFR 25–45	eGFR decline: −2.34 vs −3.61 mL/min in tolvaptan vs placebo group ($p < 0.001$)	eGFR slope: -3.16 ± 0.14 vs -4.17 ± 0.14 mL/min in tolvaptan vs placebo group ($p < 0.001$)	3	Completed and published
PA-ADPKD-301 (NCT04064346)	Lixivaptan	V2R antagonist	Age 18–60, eGFR 30–90, TKV Mayo 1C-E	eGFR	Not applicable	3	December 2024
ALADIN 1 [23] (2013)	Octreotide-LAR	Somatostatin analogue	Age > 18, mGFR ≥ 40	Mean TKV increased significantly less in the octreotide-LAR vs placebo group ($p = 0{\cdot}032$) at 1 year but not at 3 years	At 1 year TCV increased significantly less in the octreotide-LAR group ($p = 0.016$) compared with the placebo group, but not at 3 years No significant difference in NCV and GFR between the groups at 1 and 3 years	3	Completed and published

Table 1 (continued)

Clinical trials	Agent	Mechanism	Key inclusion criteria	Primary outcome/ results	Secondary outcome/ results	Phase	Estimated study completion date
ALADIN 2 [24] (2019)	Octreotide-LAR	Somatostatin analogue	Age > 18, mGFR 15–40	TKV growth reduction at 1 and 3 years ($p=0.002$) in the octreotide-LAR vs placebo group; Rate of GFR decline was not significant ($p=0.295$)	17.6% of pts in treatment group reached doubling of serum creatinine or ESRD vs 42.9% in placebo group ($p=0.0026$)	3	Completed and published
DIPAK-1 [27] (2018)	Lanreotide	Somatostatin analogue	Age 18–60, eGFR 30–60, no TKV criterion	Annual rate of eGFR decline was −3.53 vs −3.46 per year for the lanreotide vs the control group ($p=0.81$)	No significant differences for incidence of worsening kidney function, change in eGFR, and quality of life. The rate of TKV growth lower in the lanreotide than in the control group ($p=0.02$)	3	Completed and published
LIPS (NCT02127437)	Lanreotide	Somatostatin analogue	Age > 18, eGFR 30–89, no TKV criterion	eGFR month 36	eGFR month 18, safety, tolerance, onset or worsening of hypertension, quality of life, cystic pain	3	31 July 2019, not yet published
Targeting EGFr pathway							
Tesar [46] (2017)	Bosutinib	EGFr inhibitor	Pts with ADPKD, eGFR ≥ 60, TKV ≥ 750 mL	The annual rate of TKV enlargement was reduced by 66% for bosutinib vs placebo (1.63 versus 4.74%, respectively; $p=0.01$) and by 82% for pooled bosutinib vs placebo (0.84 versus 4.74%, respectively; $p<0.001$)	No statistically significant eGFR decline in patients receiving placebo or bosutinib	2	Completed and published
NCT03203642	Tesevatinib	EGFr inhibitor	eGFR 25–90, htTKV ≥ 500 mL for age 18–35; ≥ 750 mL for age 36–49; ≥ 900 mL for age 50–60	htTKV change	Safety and tolerability	2	January 31, 2022

Table 1 (continued)

Clinical trials	Agent	Mechanism	Key inclusion criteria	Primary outcome/ results	Secondary outcome/ results	Phase	Estimated study completion date
NCT01559363	Tesevatinib	EGFr inhibitor	Age 22–62, eGFR ≥ 35, htTKV ≥ 1000 mL	Safety, plasma pharmacokinetics and maximum tolerated dose, GFR	TKV	1b/2a	February 8, 2019, not yet published
Targeting AMPK pathway							
Pisani [55] (2018)	Metformin	AMP-activator protein kinase	Age 18–65, eGFR < 60	eGFR decline slowing	Loss of GFR was slower in metformin group vs placebo (−6.8 to − 3.2 mL/min/1.73 m^2 per year, p = 0.002)	Not applicable	Completed and published
TAME (NCT02656017)	Metformin	AMP-activator protein kinase	Age 18–60, eGFR > 50	Tolerability, safety	eGFR and TKV change	2	December 30, 2020
NCT02903511	Metformin	AMP-activator protein kinase	Age 30–60, non-DM, eGFR 50–80	Tolerability/safety	eGFR and TKV change	2	October 2020
METROPOLIS (NCT03764605)	Metformin	AMP-activator protein kinase	Age 18–50, non-diabetic with eGFR ≥ 45 with PKD1 truncating mutations	GFR	TKV	3	January 30, 2022
Cadnapaphornchai [60] (2014)	Pravastatin	HMG-CoA reductase inhibitor	Age 8–22, no TKV or GFR criterion	The percent change in htTKV was significantly decreased with pravastatin (23 ± 3% vs 31 ± 3%; p = 0.02)	Not applicable	3	Completed and published
NCT03273413	Pravastatin	HMG-CoA reductase inhibitor	Age 25–60, eGFR ≥ 60, TKV > 500 mL	TKV	GFR	4	December 2021
PIOPKD (NCT02697617)	Pioglitazone	PPARγ agonist	Age 18–55, non diabetic with eGFR > 50	Safety, tolerability	TKV and bone marrow fat content	2	Completed in October 2020
Targeting metabolism and diet							
Serra [72] (2010)	mTOR inhibitor	Sirolimus	Age 18–40, eGFR > 70	No effect on TKV	No effect on eGFR	3	Completed and published
Walz [71] (2010)	mTOR inhibitor	Everolimus	eGFR 30–89 or > 90 with single kidney volume > 1000 mL	TKV increase slowing down in the everolimus group at 1 year (p = 0.02) and 2 year (p = 0.06) vs placebo	No effect on eGFR	4	Completed and published
NCT03342742	Caloric restriction diet	Starvation mimicking	Age 18–65, BMI 25–45, eGFR ≥ 30	Weight loss and compliance	Tolerability, TKV	Not applicable	Completed in october 13, 2020
GREASE I [74] (2019)	Ketogenic diet	Starvation mimicking	Age 18–50, eGFR 45–89	Tolerability and safety	Not applicable	Not applicable	Completed and unpublished

Table 1 (continued)

Clinical trials	Agent	Mechanism	Key inclusion criteria	Primary outcome/ results	Secondary outcome/ results	Phase	Estimated study completion date
GREASE II [105] (2020)	Ketogenic diet	Starvation mimicking	Age 18–60, eGFR > 24, Mayo score 1C-1D-1E	TKV	GFR	2	Completed and unpublished
Targeting the KEAP1-Nrf2 pathway							
Falcon (NCT03918447)	Bardoxolone	KEAP1-Nrf2 activator	Age 18–55, eGFR 30–90; age 55–70, eGFR 30–45	Change in eGFR from baseline (52 weeks), safety	Change in eGFR from baseline (104 weeks)	3	August 2023
Targeting sphingolipids							
STAGED-PKD (NCT03523728)	Venglustat	Glucosylceramide synthase inhibitor	Age 18–50, eGFR 45–90	TKV and eGFR change	Safety and tolerability	2/3	November 2023

V2R vasopressin 2 receptor, *TKV* total kidney volume, *eGFR* estimated glomerular filtration rate, *TCV* total cyst volume, *NCV* non cyst volume, *HMG-CoA* hydroxy-3-methylglutaryl|CoA, *PPARγ* peroxisome proliferator activator receptor gamma, *mTOR* mammalian target of rapamycin, *EGFr* epidermal growth factor receptor

of 3 years of follow up was not statistically significant. Renal function decline based on iohexol was not significantly different at 1 and 3 years of follow up either [23]. ALADIN 2 recruited patients in later stages of the disease (eGFR between 15–40 mL/min/1.73 m^2) and showed a significant TKV growth reduction at 1 and at 3 years of follow-up, while the change in eGFR was not significant. Nevertheless, it is noteworthy that 17.6% of patients in the treatment group reached doubling of serum creatinine or ESRD versus 42.9% in the placebo group. The treatment has proven to be safe and well tolerated, except for some adverse gastrointestinal effects (i.e. diarrhoea, abdominal pain, cholelithiasis, and cholecystitis), and it may have a nephroprotective effect on TKV and eGFR decline [24]. Moreover, octreotide is the only available drug that reduces total liver volume [25] and prevents left ventricular dysfunction [26]. ALADIN 2 confirmed and extended the evidence from the ALADIN 1 trial that octreotide-LAR may slow kidney volume growth in ADPKD patients with normal or moderately reduced kidney function. Furthermore, it provides the novel information that a somatostatin analogue may slow the progression to ESRD in patients affected by ADPKD. This finding could have important implications for healthcare providers since the delay or even the prevention of ESRD, in addition to the improvement in the patient's quality of life and physical function, also reduces the direct and indirect costs correlated to chronic renal replacement therapy.

However, randomized controlled trials (RCTs) studying the role of somatostatin analogues in ADPKD recruited smaller populations compared to tolvaptan. The most numerically representative trial is the Developing Interventions for Polycystic Autosomal Kidney disease (DIPAK-1) study, which failed to demonstrate the ability of lanreotide to slow renal function worsening in stage 3 CKD patients affected by ADPKD [27]. The results of the Lanreotide In Polycystic Kidney Disease Study (LIPS), conducted on ADPKD patients with stages 2–3 CKD who were followed-up for 36 months after treatment with lanreotide, are awaiting publication (http://www.clinicaltrials.gov: NCT02127437) (Table 1).

The current eligibility criteria for patients who may be prescribed Tolvaptan or Octreotide are described in Fig. 3.

Standard medical therapy

Hypertension is common and occurs in the early phase of ADPKD [28]; it relates to progressive kidney enlargement and it is a significant, independent risk factor for progression to ESRD. The cilia of tubular epithelial cells, the endothelial cells and the vascular smooth muscle cells highly express PKD1 and PKD2 genes, so decreased PC1 or PC2 expression is associated with abnormal vascular structure and function. This happens through the reduction of nitric

oxide production, resulting in altered endothelial response to shear stress with the attenuation of vascular relaxation. Cyst expansion leads to intra-renal ischemia and activation of the renin–angiotensin–aldosterone system which causes hypertension, thus leading to ESRD. Therefore, inhibition of the renin–angiotensin–aldosterone system is possible with angiotensin-converting enzyme (ACE) inhibitors which are the first-line treatment for hypertension in these subjects. As suggested by the Halt Progression of Polycystic Kidney Disease (HALT-PKD) study, aggressive blood pressure control is safe and recommended and is associated with preservation of kidney function and a reduction in TKV over time [29]. A recent post hoc analysis of the HALT-PKD study showed that eGFR loss was significantly attenuated in patients with indicators of rapid progression (Mayo Classes 1D–E) [30]. A fluid intake of > 3–3.5 L/day is commonly recommended to decrease plasma osmolarity and reduce vasopressin secretion which mediates cyst growth through the cAMP pathway [31, 32]. Nevertheless, the influence of fluid intake on eGFR loss or TKV increase has not yet been determined. PREVENT-ADPKD is an ongoing RCT which aims to assess the efficacy and safety of water intake in preventing kidney failure and TKV increase in ADPKD. The study will recruit 180 patients with eGFR ≥ 30 mL/min/1.73m^2, randomized into two groups, both of which will be treated with standard therapy; patients in the control group will continue with their usual fluid intake, whereas patients in the intervention group will be prescribed enough water to maintain plasma osmolarity less than or equal to 270 mOsm/L for 36 months [33]. Limiting sodium chloride intake is generally recommended to patients suffering from CKD, and this was recently strengthened by a post hoc analysis of the HALT-PKD trial, in which urinary sodium excretion was significantly associated with kidney growth in ADPKD patients [34]. Smoking increases cardiovascular risk in CKD patients and it is associated with more rapid ADPKD progression through the increase of vasopressin secretion, as recently confirmed in a PKD1 rodent model [35, 36]. The data available from human cohorts do not indicate any effect on eGFR or TKV associated with caffeine consumption [37], therefore ADPKD patients can drink coffee but in limited amounts because it acts as a phosphodiesterase (PDE) inhibitor, which could lead to an increase of cAMP in the renal tubular epithelial cells [38].

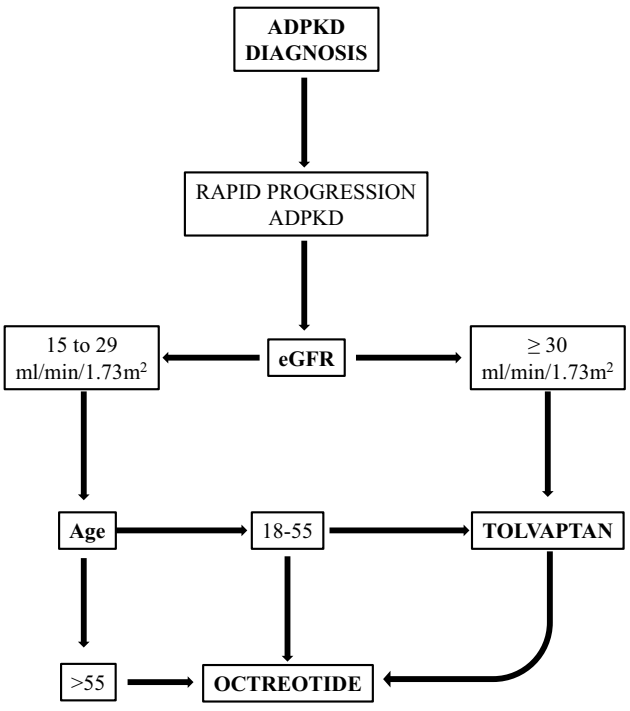


Fig. 3 Flow chart of eligibility criteria for Tolvaptan or Octreotide treatment

Therapies in development

Targeting the cAMP pathway

Lixivaptan

Lixivaptan is a novel, selective V2 receptor antagonist. Its safety and efficacy will be studied in a 52-week RCT which will enrol 1200 patients ranging from 18 to 60 years of age, withCKD stages 1–3, randomized 2:1 to oral lixivaptan twice a day or placebo for one year; the primary outcome will be eGFR assessment (http://www.clinicaltrial.gov: NCT04064346) (Table 1). Moreover, lixivaptan was predicted to have a markedly lower risk of hepatotoxicity compared to tolvaptan [39]. PCK rats treated with low-dose lixivaptan showed a 26% reduction in kidney weight/body weight ratio, a 54% reduction in kidney cystic score (a histomorphometric measure of cystic burden), a 23% reduction in kidney cAMP levels, and a 13% reduction in plasma creatinine compared to controls. A significant reduction in liver cyst burden was also reported, probably due to V2 receptor expression on cholangiocytes [40].

PDE activators

cAMP homeostasis is determined by a balance between synthesis, determined by adenylate cyclase, and degradation via PDEs [41]. Of note, a small allosteric activator of PDE4 long isoforms was recently discovered and characterized, namely, the N-substituted-2-(3-aryl-1H-1,2,4-triazol-1-yl) acetamidechemotype of MR-L2 [42] (Table 3). It reduces

intracellular cAMP levels, restrains cAMP-mediated signalling events, and profoundly inhibits the in vitro formation of kidney cysts, mimicking the stimulatory effect exerted by PKA phosphorylation on dimeric PDE4 long isoforms. These results suggest that direct pharmacological activation of PDE4 long forms may have a therapeutic function in ADPKD patients [43].

CFTR and potassium channel inhibitors

cAMP increase in ADPKD leads to the activation of CFTR channels on the apical membrane, and of potassium channels, such as Kir6.2 and Kca3.1, in the collecting ducts, resulting in the generation of a transepithelial negative electrical potential. Pharmacological inhibitors of these channels, such as TRAM-34, can delay kidney failure progression in kidney cells derived from patients with ADPKD [44]. Ouabain, a Na^+/K^+-ATPase inhibitor, also blocks cAMP-dependent fluid and anion secretion [45] (Table 3).

Targeting the EGF receptor pathway

Bosutinib

Src seems to be the key mediator of the activation and amplification of the Epidermal Growth Factor (EGF) pathway in Polycystic Kidney Disease (PKD).

Bosutinib (SKI-606) is an oral dual Src/Bcr-Abl tyrosine kinase inhibitor approved for the treatment of Philadelphia chromosome–positive chronic myeloid leukaemia in patients resistant/intolerant to imatinib. In a phase 2 study bosutinib proved to reduce kidney growth rate in patients with ADPKD, eGFR $\geq$ 60 mL/min/1.73m^2, and TKV $\geq$ 750 mL who were randomized 1:1:1 to bosutinib 200 mg/day, bosutinib 400 mg/day, or placebo for $\leq$ 24 months. However, eGFR decline, the secondary outcome, was not statistically significant at the end of 3 years of follow up. Furthermore, a large proportion of patients (200 mg/day, 45%; 400 mg/day, 84%; 400/200 mg/day, 75%; placebo, 20%) in the treatment group dropped out because of adverse effects, such as diarrhoea and nausea [46] (Table 1).

In PKD mouse and rat models, bosutinib resulted in decreased proliferation, adhesion and migration, and moreover, the number of renal cysts and kidney size were reduced. Subsequent observations confirmed that Src activity is also increased in human PKD kidneys [47].

Tesevatinib

In 2017, a double-blind RCT was initiated to compare tesevatinib vs placebo in ADPKD individuals ranging from 18 to 60 years of age, eGFR $\geq$ 25 mL/min/1.73 m^2 according to MDRD4, cysts of at least 1 cm, and height-adjusted total kidney volume (htTKV) $\geq$ 500 mL for subjects 18–35 years of age, $\geq$ 750 mL for subjects 36–49 years of age, and $\geq$ 900 mL for subjects 50–60 years of age (http://www.clinicaltrial.gov: NCT03203642). A non-randomized phase 1/2 trial completed the recruitment of 74 ADPKD patients with eGFR $\geq$ 35 mL/min/1.73 m^2 and a htTKV $\geq$ 1000 mL in order to evaluate the safety, pharmacokinetics, maximum tolerated dose and eGFR (http://www.clinicaltrial.gov: NCT01559363) (Table 1).

In mouse models of Autosomal Recessive Polycystic Kidney Disease, tesevatinib significantly inhibited multiple kinase cascades resulting in reduced phosphorylation of key mediators of cystogenesis such as EGFR, ErbB2, c-Src and KDR [48].

Anti-vascular endothelial growth factor (VEGF) antibodies

ADPKD anomalies include vascular malformations with an extensive capillary network in the cyst wall, increased VEGF165 expression in cyst cells and increased VEGF receptor 2 (VEGFR2) expression in endothelial cells. A possible role of angiogenesis in the early progression of the disease was confirmed by a clinical study that showed a strong correlation between angiogenic growth factors and both renal and cardiac disease severity [49]. In animal models, inhibition of the mRNA expression of VEGFR1 and 2 led to a significant decrease in tubular cell proliferation, cystogenesis, renal enlargement and renal function loss [50].

However, a different study reported that B20.4.1, an anti-VEGF-A antibody, increased cell proliferation and cyst growth in a rat model [51] (Tables 2, 3).

Targeting AMP-activator protein kinase

Metformin

Metformin, which is widely used in type 2 diabetes and polycystic ovary syndrome, has been proposed as a novel therapy for early stages of ADPKD as it acts on the metabolic sensor AMP-activated protein kinase (AMPK). AMPK is activated under conditions of metabolic and other cellular stress and it decreases cellular energy consumption. Furthermore, AMPK phosphorylates and inhibits CFTR, thus suppressing epithelial fluid and electrolyte secretion. Similarly, AMPK phosphorylates tuberin protein, leading to indirect

Table 2 Animal studies targeting calcium cell regulation, cell cycle, EGFr, MAPK, AMPK pathways, epigenetic DNA, interstitial inflammation, cell therapy

Agent	Mechanism	Trial	Key inclusion criteria	Outcome/results
Targeting calcium cell regulation				
4αPDD GSK1016790	TRPV4 channel activators	Gradilone [82] (2010)	PCK rats	Reduction of renal cyst development and fibrosis
R568	CaSR selective modulator	Gattone [84] (2009)	Han:SPRD Cy/+rats, pcy mice	Cyst growth and fibrosis inhibition
R568	CaSR selective modulator	Chen [83] (2011)	PCK rats and Pkd2−/WS25 mice	No effect on cyst growth
Triptolide	calcium release induction from endoplasmic reticulum	Leuenroth [87, 88] (2007, 2008)	PKD1−/− cells in mouse model	Cyst growth inhibition
Targeting cell cycle				
R-roscovitine S-CR8	CDK inhibitors	Bukanov [89] (2012)	PCK mice, PKD1 KO mice	Renal and hepatic cystic index reduction
Menadione	Cdc25A inhibitor	Masyuk [90] (2012)	PCK rats and Pkd2ws25/− mice	Renal and hepatic cyst growth inhibition
Targeting EGFr pathway				
B20.4.1	anti-VEGF-A antibody	Raina [51] (2011)	Heterozygous (Cy/+) Han:SPRD rats	Increased PTEC proliferation and cystogenesis
Targeting MAPK pathway				
PLX5568	B-Raf kinase inhibitor	Buchholz [93] (2011)	Han: SPRD rats	Cyst enlargement attenuation, no effect on TKV and GFR
PD184352	MEK inhibitor	Calvet [94] (2006)	pcy mouse	Cyst growth inhibition
PD184352	MEK inhibitor	Okumura [95] (2009)	inv mutant mice	Cystogenesis decrease and kidney function improvement
NVP-BEZ235	Dual mTOR/PI3K inhibitor	Liu [96] (2018)	Heterozygous (Cy/+) Han: SPRD rats, Pkd1 conditional ko mouse	Reduced cell proliferation, cyst growth, interstitial fibrosis
Targeting AMPK pathway				
2-Deoxyglucose	Glycolysis competitive inhibitor	Chiaravalli [69] (2016)	Orthologous and PKD mice models	Disease progression slowing down
2-Deoxyglucose	Glycolysis competitive inhibitor	Riwanto [70] (2016)	Orthologous mouse model	Cystic disease progression
Targeting epigenetic DNA				
Valproic acid	Class I HDAC inhibitor	Cao [97] (2009)	Pkd1 and Pkd2 knockout mice	Cyst growth inhibition
TrichostatinA	Pan-HDAC inhibitor	Fan [98] (2012)		Cyst formation suppression
Tubacin	HDAC6 inhibitor	Cebotaru [99] (2016)	Pkd2 knockout mice	Cystogenesis prevention
ACy-1215	HDAC6 inhibitor	Yanda [100] (2017)	Pkd1-conditional mouse model Pkd1 mice	Slow renal cyst growth
Targeting interstitial inflammation				
Bindarit	MCP-1/CCL2 synthesis inhibitor	Zoja [101] (2015)	PCK rats	Interstitial inflammation and renal failure reduction
Etanercept	TNF-α inhibitor	Li [102] (2008)	Pkd2+/− mice	Inhibit cyst formation
Cell therapy				
Cell therapy	Allogenic MSCs tranplantation	Franchi [104] (2015)	PKD rat model	Kidney function and damaged vasculature improvement

TRPV4 transient receptor potential vanilloid 4, *CaSR* calcium sensing receptor, *CDK* cyclin-dependent kinase, *MCP-1/CCL2* monocyte chemoattractant protein-1/C–C, *MSCs* mesenchymal stem cells, *TNF-α* tumor necrosis factor-alfa

Table 3 Culture cell studies targeting cAMP, AMPK, and MAPK pathways, epigenetic DNA, interstitial inflammation

Agent	Mechanism	Trial	Key inclusion criteria	Outcome/results
Targeting cAMP pathway				
MR-L2	PDE4 long forms activator	Omar [42] (2019)	MDCK cells	Cyst growth inhibition
TRAM-34	KCa3.1 channels inhibitor	Albaqumi [24] (2008)	MDCK and ADPKD cells	Cyst formation inhibition
Ouabain	Na+, K+-ATPase inhibitor	Nguyen [45] (2007)	Polarized ADPKD cell monolayers	cAMP-dependent net fluid secretion inhibition
Targeting EGFr pathway				
B20.4.1	anti-VEGF-A antibody	Raina [51] (2011)	in vitro	Increased PTEC proliferation, cystogenesis, proteinuria severe renal failure, and glomerular damage
Targeting AMPK pathway				
Metformin	AMP-activator protein kinase	Takiar [52] (2011)	MDCK cells	Ex vivo and in vivo cystogenesis slowing
Targeting MAPK pathway				
Sorafenib	B-Raf kinase inhibitor	Yamaguchi [92] (2010)	Human ADPKD cells ko PKD2	Cyst growth inhibition, liver cyst area and cell proliferation increase
PLX5568	B-Raf kinase inhibitor	Buchholz [93] (2011)	MDCK cells Human ADPKD cells	Cyst growth was significantly reduced Cyst growth and cell proliferation inhibition, no effect on TKV and GFR
NVP-BEZ235	Dual mTOR/PI3K inhibitor	Liu [96] (2018)	in vitro culture of primary cells	Reduced cell proliferation, cyst growth, kidney weight, and improved BUN, SCr, urine albumin/creatinine ratio
Targeting epigenetic DNA				
Tubacin	HDAC6 inhibitor	Cebotaru [99] (2016)	MDCK cells	Cystogenesis prevention
ACy-1215		Yanda [100] (2017)	MDCK cells and PKD1-null and heterozygous cells	HDAC6 activity reduction and cAMP levels downregulation
Targeting interstitial inflammation				
Celecoxib	COX-2 inhibitor	Xu [103] (2012)	Cyst-lining epithelial cells from patients with ADPKD	VEGFR-2 and Raf-1 expression inhibition, thereby, reduced inflammation and fibrosis

PDE4 phosphodiesterase 4, *MDCK* Madin–Darby canine kidney cells, *EGFr* epidermal growth factor receptor, *PTEC* tubular epithelial cell, *HDAC* histone deacetylases, *PKD* polycystic kidney disease, *HDAC* histone deacetylases, *COX-2* cyclooxygenase-2, *VEGF* vascular endothelial growth factor

inhibition of the mTOR pathway. Metformin slowed cystogenesis in two mouse models and in a zebrafish model of ADPKD [52, 53]. We recently reported the beneficial effect of metformin on ADPKD progression in the same family, confirming our previous results on the effect of metformin in delaying renal progression in ADPKD patients with moderately impaired eGFR [54, 55]. In a phase 2 active but not recruiting RCT (TAME) on the safety and tolerability of metformin compared to placebo in early stages of ADPKD (eGFR > 50 mL/min/1.73 m^2), 97 non-diabetic patients aged from 18 to 60 years will be enrolled and followed-up for 26 months (http://www.clinicaltrial.gov: NCT02656017). A second phase 2 recruiting RCT will enrol 50 ADPKD non-diabetic patients aged between 30 and 60 years of age and eGFR between 50 and 80 mL/min/1.73m^2; the primary outcome is the change in TKV and eGFR (http://www.clinicaltrial.gov: NCT02903511). The Metformin vs Tolvaptan for Treatment of Autosomal Dominant Polycystic Kidney Disease (METROPOLIS) study, a phase 3 RCT, will enrol 150 non-diabetic patients ranging from 18 to 50 years of age, with eGFR ≥ 45 mL/min/1.73 m^2 and truncating mutations of the PKD1 gene, who will be randomized to metformin or tolvaptan and followed-up for 25 months in order to assess the variations in TKV and GFR (http://www.clinicaltrial.gov: NCT03764605) (Table 1).

Statins

Statins are hydroxy-3-methylglutarylCoA (HMG-CoA) reductase inhibitors which also seem to have anti-cystic effects due to AMPK activation, though the mechanisms are yet to be elucidated [56]. They ameliorated cystic phenotypes in ADPKD animal models as well as in clinical trials in paediatric patients with early-onset ADPKD [57–59]. This effect was confirmed in a paediatric double-blind phase 3 RCT examining pravastatin versus placebo in 110 children [60]. However, a recent post hoc analysis of the HALT-PKD trial regarding statin use did not show any beneficial effect [61]. Thus, an ongoing RCT will assess the efficacy and benefits of pravastatin therapy in 150 adults with ADPKD (eGFR $\geq$ 60 mL/min/1.73m^2, 25–60 years old) after 2 years of treatment by evaluating TKV through magnetic resonance imaging and renal blood flow measured by kidney magnetic resonance angiography (http://www.clinicaltrial.gov: NCT03273413) (Table 1).

Thiazolidinediones (TZDs)

TZDs are Peroxisome Proliferator Activator Receptor gamma (PPARγ) agonists, used to treat metabolic syndrome and type 2 diabetes mellitus; they can also inhibit cell proliferation via extracellular signal-regulated kinase (ERK) signalling, fibrosis, and inflammation through reduction of Transforming Growth Factor beta (TGF-β) levels [62, 63]. A combination of tolvaptan and pioglitazone showed better results than tolvaptan alone in an adult-onset PKD mouse model. Pioglitazone efficacy varies substantially between PKD models and species most likely because of several potential pharmacokinetic and pharmacodynamic differences [64]. Based on these results, a phase 2 clinical trial was designed to investigate low-dose pioglitazone safety and efficacy in slowing ADPKD progression (http://www.clinicaltrial.gov: NCT02697617) (Table 1). Maternal administration of high-dose pioglitazone ameliorated the cystic phenotype of Pkd1−/− mouse embryos and improved their survival [65]. The slowing effect of TZDs on PKD disease progression has also been shown in a PCK rat model [66]. Pioglitazone also reduced CFTR gene expression in in vitro models [67].

2-deoxyglucose (2DG)

Defective glucose metabolism is assumed to play a role in cystogenesis; in fact, cyst epithelial cells avidly consume glucose and are highly dependent on its availability to sustain their growth, being particularly sensitive to even small reductions in glucose levels. Glycolysis can be inhibited by 2DG, which is transported into the cells but cannot undergo glycolysis, acting as a competitive inhibitor of the glycolytic pathway. Consistent with this hypothesis, cells with mutated pkd1 switched to anaerobic glycolysis for energy production (the "Warburg effect") in a PKD mouse model [68]. Chronic administration of low-dose 2DG was able to prevent disease progression in two slowly progressive, orthologous disease models [69] (Table 2). Furthermore, 2DG slowed the progression of cystic disease in an orthologous mouse model of ADKPD [70].

Targeting metabolism and diet

mTOR inhibitors

Despite promising pre-clinical results, an everolimus study [71] on 433 relatively advanced patients as well as a sirolimus study [72] on 100 patients at an earlier stage showed no effects on TKV and eGFR (Table 1). A metanalysis of 9 RCTs enrolling 784 ADPKD patients receiving rapamycin, sirolimus, or everolimus showed that mTOR inhibitors did not significantly influence renal progression, but were associated with a higher risk of complications [73]. Studies in ADPKD rodent models showed that mTOR inhibitors induced a significant and long-lasting decrease in kidney volume, and improved kidney function.

Caloric restriction diet

A RCT will be conducted on 28 overweight/obese ADPKD adults (eGFR $\geq$ 30 mL/min/1.73m^2 according to Chronic Kidney Disease Epidemiology Collaboration equation; 18–65 years) to determine the feasibility of a 1-year behavioural weight loss intervention program based on either daily caloric restriction or intermittent fasting with a similar (~34%) targeted weekly energy deficit. Key secondary goals are safety and tolerability of intermittent fasting in ADPKD versus daily caloric restriction, and changes in TKV assessed by magnetic resonance imaging (http://www.clinicaltrial.gov: NCT03342742). Recently, a pilot study on the administration of a ketogenic diet in patients affected by Autosomal Dominant Polycystic Kidney Disease (GREASE1) evaluated the feasibility of a ketogenic diet in ADPKD on three patients for three months: there was good compliance, glycaemia decreased significantly, while the most important side effect was an increase in cholesterol levels [74] (Table 1). In ADPKD rodent models, mild-to-moderate food restriction slowed cyst growth and maintained renal function via mechanisms including AMPK activation, suppression of mTOR/S6 kinase signalling and insulin-like growth factor-1 levels [75].

Targeting the KEAP1-Nrf2 pathway

Bardoxolone

Under basal conditions, nuclear factor erythroid 2-related factor 2 (Nrf2) is sequestered in the cytoplasm via binding to Kelch-like ECH-associated protein 1 (Keap1). During exposure to oxidants, the interaction between Keap1 and Nrf2 is disrupted, so Nrf2 translocates to the nucleus and binds antioxidant response element, increasing antioxidant enzyme transcription. Moreover, Nrf2 is involved in the cross-talk with the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [76]. Bardoxolone methyl is a Nrf2 activator that increased eGFR in patients with type 2 diabetes and stage 3 CKD in the randomized, placebo-controlled 52-Week Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM trial) [77]. The Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (Beacon trial), a phase 3 RCT designed to determine whether bardoxolone would reduce ESRD and cardiovascular events in patients with CKD and type 2 diabetes, was previously discontinued because of disproportionate heart failure hospitalizations among those assigned to the bardoxolone group [78]. The Falcon study is a phase 3 RCT which will study the safety, tolerability, and efficacy of bardoxolone methyl in ADPKD patients with eGFR 30–90 mL/min/1.73 m^2 (18–55 years) or 30–44 mL/min/1.73 m^2 (56–70 years), enrolling approximately 300 patients randomized 1:1 to either bardoxolone methyl or placebo;primary and secondary outcomes will be eGFR change from baseline to 52 and 104 weeks, respectively (http://www.clinicaltrial.gov: NCT03918447) (Table 1). In an orthologous ADPKD mouse model, genetic deletion of Nrf2 increased reactive oxygen species generation and promoted cyst growth, whereas pharmacological induction of Nrf2 reduced reactive oxygen species production and slowed cystogenesis and disease progression [79].

Substrate reduction therapy against sphingolipids: glucosylceramide synthase inhibitors

Venglustat

Mutations in PCs lead to target of rapamycin kinase complex 1 and 2 activation, causing de novo ceramide synthesis; in addition, PC dysregulation leads to target of rapamycin kinase complex 2 activation, which not only promotes de novo ceramide synthesis but also increases glucosylceramide production. Glycosphingolipid accumulation in PKD disrupts signalling activity and promotes loss of differentiation and proliferation due to increased cell cycle progression resulting in cyst formation and growth [80]. Venglustat is a potent oral inhibitor of glucosylceramide synthase, the enzyme that synthesizes sphingolipids, including glucosylceramide. Since October 2018, a Medical Research Study Designed to Determine if Venglustat Can be a Future Treatment for ADPKD Patients (STAGED-PKD) trial is recruiting rapidly progressive ADPKD patients with eGFR 45–90 mL/min/1.73 m^2 who are 18–50 years of age in order to assess effectiveness and safety of venglustat in 2 years of follow up. In the first stage, a subset of the trial population will be analysed for the treatment effect on htTKV. In the second stage, all subjects will be analysed for the treatment effect on eGFR (http://www.clinicaltrial.gov: NCT03523728) (Table 1). Animal models showed a significant increase in glucosylceramide and ganglioside GM3 plasma levels in PKD, and treatment with glucosylceramide synthase inhibitors reduced cystic disease progression [81].

Targeting intracellular calcium regulation

TRPV4 channel activators

Transient Receptor Potential Vanilloid 4 (TRPV4) is a calcium entry channel acting as an osmosensor, being activated by extracellular hypo-osmolarity and inhibited by extracellular hyperosmolarity. TRPV4 is over-expressed in the PCK rat and PKD human liver. Its pharmacologic activation by 4αPDD and GSK1016790 increases intracellular calcium, resulting in in vitro cholangiocyte proliferation inhibition and in vivo cyst growth reduction by a mechanism involving the Akt and B-Raf/Erk1/2 signalling pathway [82] (Table 2).

Calcimimetics

Calcium-sensing receptor (CaSR) activation is associated with cAMP signalling reduction and intracellular calcium increase. Therefore, type 2 calcimimetic drugs, acting as positive allosteric CaSR modulators, were suggested for ADPKD treatment. Calcimimetic R568 was tested in mouse models and significantly reduced kidney weight [83] and renal cyst growth [84] (Table 2). Recently, increased intracellular calcium and reduced intracellular cAMP and mTOR activity was observed in human conditionally immortalized Proximal Tubular Epithelial cells carrying the PKD1 mutation after selective CaSR activation [85].

Triptolide

Triptolide is a natural product isolated from the traditional Chinese medicine *Tripterygium wilfordii* (also known as "Thunder

God Vine" or Lei Gong Teng), used for inflammatory and autoimmune disorders and, due to its concentration-dependent anti-proliferative and pro-apoptotic properties, as a potent chemotherapeutic agent through the inhibition of NF-kB and NF-AT-mediated transcription [86]. In Pkd1−/− embryonic mice, triptolide induced cellular calcium release from the endoplasmic reticulum through a PC2-dependent pathway, arrested Pkd1−/− cell growth and reduced cystic burden [87]. In another mouse model, it significantly improved cyst growth and renal function at postnatal day 8; however, it presented side effects such as infertility and immunosuppression [88] (Table 2).

Targeting cell cycle regulation

CDK inhibitors

There is a direct link between primary cilium, centrosomes and cell cycle dysregulation in PKD. PC2 can bind Id2, a protein regulating cell proliferation and differentiation, and it prevents its translocation into the nucleus blocking cell cycle progression. Instead, PC1 directly arrests cell cycle by inhibiting cyclin-dependent kinase (CDK)2 activity through up-regulation of p21. In an orthologous model of ADPKD with a conditionally inactivated pkd1 gene, two different CDK inhibitors (R-roscovitine and S-CR8) reduced cystic kidney disease progression and functional decline as well as liver cystogenesis [89] (Table 2).

Menadione

Cell division cycle 25 A (Cdc25A) phosphatase over-expression is another factor affecting PKD cell-cycle deregulation. Cdc25A inhibition by menadione (vitamin K3) in animal models blocked cell cycle progression and proliferation, thus reducing liver and kidney weight and cyst growth [90] (Table 2).

Targeting MAPK pathway

Raf kinase inhibitors

Cell proliferation in cystic epithelial cells is induced by MEK/ERK pathway activation due to the differences in calcium concentration between cystic and normal kidney cells. Raf kinases are part of the MAPK cascade activating the MAPK–ERK kinase MEK; MEK then activates ERK, and phosphorylated ERK translocates to the nucleus where it regulates various transcription factors [91].

Sorafenib (Bay 43-9006) is a multikinase inhibitor used for the treatment of advanced renal cell and hepatocellular carcinomas. At nanomolar concentrations it acts as a B-Raf inhibitor, suppressing MEK/ERK signalling, cell proliferation, and in vitro cyst growth of human ADPKD cells stimulated by cAMP and/or EGF [92]. PLX5568, a novel selective small molecule inhibitor of Raf kinases, attenuated cyst enlargement in vitro and in a rat model of ADPKD without improving kidney function, presumably due to increased renal fibrosis [93] (Tables 2, 3).

MEK inhibitors

The MAPK/ERK inhibitor PD184352, was shown to effectively block cyst growth and kidney enlargement and to preserve renal function when given to pcy mice affected by nephronophthisis, an adolescent form of recessive PKD [94]. PD184352 also successfully decreased ERK levels, inhibited renal cyst enlargement and decreased expression of cell-cycle regulators in Inv mice, a model for human nephronophthisis type 2 characterized by multiple renal cysts and situs inversus [95] (Table 2).

Dual mTOR/PI3K inhibitor

mTOR inhibitors up-regulate pro-proliferative phosphatidylinositol 3-kinase (PI3K)-Akt and PI3K-ERK signalling in murine PKD models. Dual mTOR/PI3K inhibition with NVP-BEZ235 interrupts these pro-proliferative signals and normalizes kidney morphology and function by blocking proliferation and fibrosis [96] (Tables 2, 3).

Targeting epigenetic DNA

HDAC inhibitors

Histone deacetylase 6 (HDAC6) expression and activity is increased in Pkd1-mutant renal epithelial cells and could play a role in cyst formation. Valproic acid is a class I HDAC inhibitor which decreased kidney cyst growth in Pkd2-deficient mice; trichostatin A, a pan-HDAC inhibitor, suppressed cyst formation by regulating cell proliferation in Pkd2 knockout mice [97]; tubacin and ACy-1215 are specific HDAC6 inhibitors which prevented in vitro cyst formation in PKD models [98–100] (Tables 2, 3).

Targeting interstitial inflammation

Interstitial inflammation is a cause of cyst progression, and PKD genes can regulate the expression of pro-inflammatory chemo-attractants such as monocyte chemoattractant protein-1 (MCP-1); in fact, macrophages are the principal component of inflammatory infiltrate in both human and animal models of PKD. Bindarit is an inhibitor of MCP-1/CCL2 synthesis, and in PCK rats, it ameliorated PKD evolution [101]. Other therapeutic approaches targeting inflammatory cytokines are etanercept, a tumor necrosis factor-alpha (TNF-α) inhibitor [102], and celecoxib, a highly selective

cyclooxygenase 2 (COX-2) inhibitor, which prevented human cyst-lining epithelial cell growth [103] (Tables 2, 3).

Cell therapy

A single intravenous infusion of allogenic mesenchymal stem cells in a PKD rat model had a beneficial effect on systolic hypertension, fibrosis, cortical and parenchymal vasculature density, but no effect on cyst size and number [104] (Table 2). These favourable effects occur through different mechanisms, including p38 MAPK inhibition, NF-κB pathway and pro-inflammatory cytokine interference. Moreover, mesenchymal stem cells inhibit the renin–angiotensin–aldosterone system in a more stable manner than ACE inhibitors through the reduction of renin, ACE, and angiotensin II type 1 receptor expression.

Conclusions

Treatment of ADPKD still represents a challenge for both clinicians and researchers as concerns have been raised regarding the tolerability, toxicity, and real impact the available drugs (i.e. tolvaptan and octreotide-LAR) have on renal disease progression. Many preclinical models have provided new therapeutic targets, but they do not perfectly represent the human disease and may not thoroughly predict the clinical efficacy of tested molecules. Consequently, clinical research plays a pivotal role in really understanding the potential therapeutic effects of new drugs. Fortunately, encouraging results are expected from ongoing clinical trials testing novel promising molecules, such as lixivaptan (PA-ADPKD-301), bardoxolone (FALCON), metformin (METROPOLIS, TAME), pravastatin (NCT03273413) and venglustat (STAGED-PKD); while results of the RCTs on lanreotide (LIPS), pioglitazone (PIOPKD) and tesevatinib (NCT01559363) are awaiting publication. In the nearfuture, the findings of these studies will definitely help clinicians in the challenging efforts to modify the dramatic natural history of ADPKD.

Funding No funds, Grants, or other support was received.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the contents of this article.

Ethical statement For this type of study (i.e. review article) ethical approval is not required.

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