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REVIEW ARTICLE

Drugs in Clinical Development to Treat Autosomal Dominant Polycystic Kidney Disease

Thomas Bais[1] · Ron T. Gansevoort[1] · Esther Meijer[1]

Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cyst formation that ultimately leads to kidney failure in most patients. Approximately 10% of patients who receive kidney replacement therapy suffer from ADPKD. To date, a vasopressin V2 receptor antagonist (V2RA) is the only drug that has been proven to attenuate disease progression. However, aquaresis-related adverse events limit its widespread use. Data on the renoprotective effects of somatostatin analogues differ largely between studies and medications. This review discusses new drugs that are investigated in clinical trials to treat ADPKD, such as cystic fibrosis transmembrane conductance regulator (CFTR) modulators and micro RNA inhibitors, and drugs already marketed for other indications that are being investigated for off-label use in ADPKD, such as metformin. In addition, potential methods to improve the tolerability of V2RAs are discussed, as well as methods to select patients with (likely) rapid disease progression and issues regarding the translation of preclinical data into clinical practice. Since ADPKD is a complex disease with a high degree of interindividual heterogeneity, and the mechanisms involved in cyst growth also have important functions in various physiological processes, it may prove difficult to develop drugs that target cyst growth without causing major adverse events. This is especially important since long-standing treatment is necessary in this chronic disease. This review therefore also discusses approaches to targeted therapy to minimize systemic side effects. Hopefully, these developments will advance the treatment of ADPKD.

1 Introduction

Autosomal dominant polycystic kidney disease (ADPKD) typically leads to progressive cyst formation in the kidneys, which causes kidney enlargement (shown in Fig. 1), pain, hematuria, and progressive loss of kidney function that ultimately leads to kidney failure [1]. In addition to local manifestations in the kidney, the disease is associated with systemic manifestations such as hypertension; cyst formation in the liver, pancreas and spleen; valvular heart disease; and intracerebral aneurysms. Although ADPKD has an estimated prevalence of around 4:10,000 [2] and is therefore not very common, the disease is seen quite frequently in clinical routine because of its progressive character. It is estimated

Key points

The pathophysiology of ADPKD is complex and various potential therapeutic targets are available for which novel treatments are being developed or repurposed, but as yet V2RAs are currently the only widely accepted renoprotective treatment for this disease.

Because ADPKD is a chronic disease that requires lifelong treatment, and targets involved in cyst growth also have important functions in various physiological processes, there is a need to develop (targeted) therapies to minimize systemic side effects.

Since various treatment options have shown discrepant results between preclinical and clinical studies, we suggest the use of at least 2 different rodent polycystic kidney disease models before proceeding to clinical trials or before aborting drugs for clinical use.

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that around 10% of patients who are on kidney replacement therapy suffer from ADPKD [3].

In the majority of ADPKD patients, the disease is caused by a mutation in the *PKD1* or *PKD2* gene. To date, approximately 1500 different pathogenic mutations in the *PKD1* and *PKD2* genes have been recorded. The *PKD1* gene, located on chromosome 16, encodes the polycystin 1 protein, and mutations in this gene account for around 78% of ADPKD cases [5]. The *PKD2* gene is located on chromosome 4 and encodes the protein polycystin 2 [6]. Polycystin 1 and 2 form a complex that is located on the primary cilia of renal tubular cells. This complex is thought to be involved in transmission of information from the external environment to the cell. The idea is that polycystin 1 and 2 inhibit cystogenesis in a dose-dependent way, and that cystogenesis occurs when the concentration of polycystin 1 or 2 falls below a critical threshold [7, 8]. More recently identified mutations, such as mutations in the *GANAB* gene [9] and the *DNAJB11* gene [10], as well as mutations in genes associated with polycystic liver disease (*PRKCSH, SEC63, LRP5, ALG8,* and *SEC61B*), lead to maturation defects of polycystin 1 and 2 [11]. These maturation defects interfere with the attainment of a fully functional and appropriately localized polycystin complex [12]. When concentrations of polycystin 1 or 2 fall below the aforementioned threshold, the intracellular calcium concentration decreases, leading to, among others, increased cyclic AMP (cAMP) concentrations in renal tubular cells and ultimately to cystogenesis through activation of proliferative signaling pathways.

In this review, we discuss new treatment options that are under investigation in clinical trials as well as some issues that merit attention when developing drugs to treat ADPKD, namely which patients are at risk of rapid disease progression and should be treated, study sample size considerations, potential solutions to reduce side effects of current and upcoming treatment options, and the problems that are faced when extrapolating data from animal models to the human situation. Relevant articles and trials were selected from three online databases (PubMed, Clinicaltrials.gov and the Cochrane Central Register of Controlled Trials) using as search terms ("ADPKD" OR "PKD") AND ("treatment" OR "therapy"), with a focus on recent works from 2010 up until April 2022. For an overview of symptomatic treatment of hypertension and other cardiovascular complications of ADPKD, as well as of non-pharmacological options and treatment of polycystic liver disease, we refer to other recent review articles [13–15].

2 Selection of Patients for Treatment (in Trials) and Sample Size Considerations for Interventional Autosomal Dominant Polycystic Kidney Disease (ADPKD) Trials

The disease course of ADPKD is highly variable. Some patients develop rapid kidney enlargement and subsequent progression to end stage kidney disease (ESKD) at a young age, while others will never develop significant renal impairment. The inclusion of patients with rapidly progressive disease in clinical trials ensures that beneficial effects on endpoints like total kidney volume (TKV) growth or renal function decline can be detected. Identifying patients at risk for rapidly progressive disease is also necessary in clinical practice to select patients who will benefit the most from treatment, and to protect patients who do not require treatment against treatment-related costs and side effects.
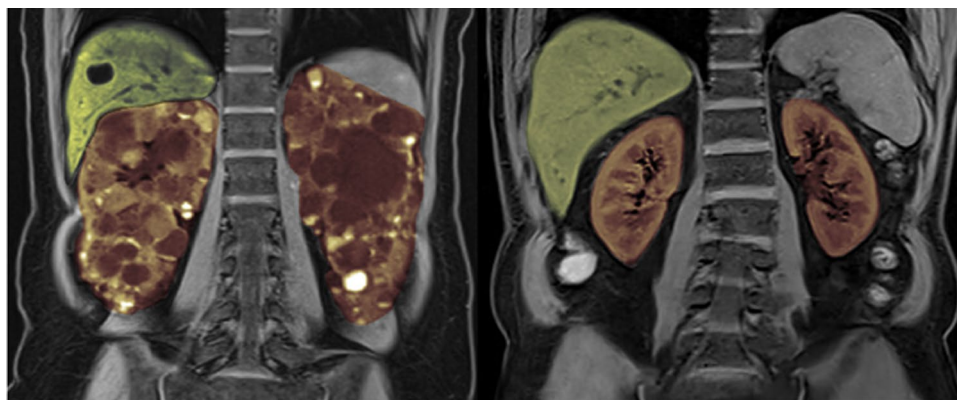
Fig. 1 MRI scan of a 33-year-old female with autosomal dominant polycystic kidney disease (ADPKD). Innumerable cysts are present throughout both kidneys (depicted in orange), and a few cysts are present in the liver (depicted in green). The total kidney volume (TKV) of this patient is 1800 mL; roughly eight times larger than normal. Two normal sized kidneys are shown on the right for reference (normal MRI-measured TKV in females: approximately 260–300 mL [4])

There is no international consensus on the definition of rapidly progressive ADPKD [16]. The European Renal Association (ERA) has recently published an updated position statement regarding in which ADPKD patients to prescribe tolvaptan [17]. This paper defines rapidly progressive disease as an annual estimated glomerular filtration rate (eGFR) decline of ≥ 3.0 mL/min/1.73 m^2. That cut-off value was chosen based on the observed rates of eGFR decline in unselected cohorts of ADPKD patients [18]. An algorithm is presented to identify patients who in the future will likely show an eGFR loss that is more rapid than this cut-off, i.e., have rapidly progressive disease. This algorithm relies on several indicators of disease severity like kidney function indexed for age, historical kidney function decline, Mayo Clinic classification, and the PROPKD score. These disease severity indicators are also used to select patients with rapidly progressive disease for inclusion in clinical ADPKD trials that investigate the renoprotective efficacy of other drugs. Individually, the predictive value of these disease severity indicators is relatively limited [19], but integrating multiple disease indicators will likely improve the predictive capacity and should be considered when developing similar algorithms. Several plasma or urinary biomarkers have also been investigated for this purpose, for example plasma copeptin [19] and urinary monocyte chemoattractant protein-1 excretion [20], but reliable algorithms that incorporate these biomarkers are not yet available. The development of such an algorithm would be a substantial advancement, especially to enable selection of rapidly progressive patients early in the disease course (when kidney function is still intact) and to further refine risk assessment for patients in whom volumetric indices are ambiguous (e.g., patients with Mayo class 1C, of whom at least half will have an annual rate of eGFR loss of less than 3.0 mL/min/1.73 m^2) [21].

The required sample size for clinical trials depends on a number of factors, including two fixed assumptions, namely the chance of making a type I error (i.e., the chance of reaching a false positive conclusion, that is typically set at 5% or an α of 0.05) and the chance of a type II error (i.e., the chance of reaching a false negative conclusion, that is usually set at 20%, or a β of 0.20). In addition to these assumptions, the required number of patients also depends on the expected treatment effect on the decline of eGFR, which in the field of nephrology, including PKD, is often set at a reduction of 30% [22–24]. Although TKV can be used as a surrogate outcome that may even be used to obtain conditional drug approval, a trial with eGFR decline as the primary endpoint should always be performed, since renoprotection is the ultimate goal of ADPKD treatment. The study sample size also depends on the incidence of the outcome and its variance. This re-emphasizes that inclusion of rapidly progressive ADPKD patients is important to be able to detect a treatment effect. As an example, it can be calculated that for a phase 3 clinical ADPKD trial with an α of 0.05 and β of 0.20 (a power of 80%), assuming a mean eGFR decline of -3.5 mL/min/1.73 m^2 per year in the placebo group [22, 25, 26], with a standard deviation of ± 3.0 mL/min/1.73 m^2 per year and an estimated treatment effect of 30%, a total sample size of 256 patients would be appropriate. When, for instance for registration purposes, a more stringent β is used (0.13) and adjustments are made to account for dropout rate, multiplicity of tests and an interim analysis, in total 560 patients would be needed. This number was calculated for the STAGED-PKD trial [23], of which the design was US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved.

In hindsight, it therefore seems that some ADPKD trials that have been performed, most notably the TEMPO 3:4 and REPRISE trials [25, 26], were vastly overpowered. As stated in the power calculation for the TEMPO 3:4 trial [27], the adopted α, β and estimated treatment effect were more stringent than usual (0.045, 0.15, and 20%, respectively). Even with these figures, only 504 patients were calculated to be necessary. However, it was stated in the power calculation that this number was doubled to enroll 1200–1500 patients to provide a higher than usual degree of statistical significance for the primary endpoint and to be able to evaluate a plethora of secondary endpoints [27]. After completion of the TEMPO 3:4 trial, it appeared that all p-values for the primary and most secondary endpoints were extremely small, even in subgroups, indicating that the trial was indeed overpowered. Unfortunately, despite being of great importance to the field of ADPKD, this trial can lead to the unjustified assumption that ADPKD trials should typically include this large number of patients. As reasoned above, conventional power analyses show that considerably lower numbers should be sufficient.

3 Currently Available Treatments

Increasing knowledge of the underlying pathophysiology of the disease has laid the basis for the development of new potential therapeutic targets. Table 1 depicts the landmark clinical trials performed in ADPKD so far. Unfortunately, many of these therapeutic targets are involved not only in cyst formation, but also in numerous physiological processes throughout the body that are important for cellular proliferation, growth, and repair. Drugs that target these processes may therefore lead to severe adverse effects that limit their utility. An example of this is the mammalian target of rapamycin (mTOR) pathway. For the mTOR pathway, two landmark trials were published in 2010 that investigated inhibition of this pathway with everolimus and sirolimus in early- [28] and later-stage [29] ADPKD. While animal studies were promising, both clinical studies

produced disappointing results, probably because side effects, such as mucositis and diarrhea, limited the use of higher dosages that are needed to achieve effect. In a similar fashion, the somatostatin analogues lanreotide and octreotide have shown efficacy in animal studies. However, several clinical studies that investigated somatostatin analogues reported conflicting results in ADPKD patients [22, 30, 31]. For instance, the ALADIN trial [30] investigated the effect of octreotide long-acting release (LAR) versus placebo in 79 ADPKD patients (eGFR ≥ 40 mL/min/1.73 m^2) with change in TKV as primary endpoint. Octreotide LAR significantly reduced TKV growth after 1 year but not at 3 years. The effects on kidney function are more complex to interpret. The decline in measured GFR from baseline to year 3 was not significantly different in the octreotide LAR group compared to placebo, but it was significant when measured from year 1 to 3. Unfortunately, despite careful randomization, patients in the placebo group appeared to have more severe disease, making it complicated to draw conclusions. The ALADIN 2 trial [31] investigated octreotide LAR versus placebo in 100 ADPKD patients with later-stage disease (eGFR 15–40 mL/min/1.73 m^2), with TKV growth and measured GFR decline as primary endpoints. In this study, octreotide LAR significantly reduced TKV growth at 1 and 3 years, but there was no significant effect on measured GFR decline (neither when measured as slope from baseline to year 3, nor as slope from year 1 to 3). Despite the lack of effect on measured GFR decline, patients treated with octreotide LAR progressed less frequently to a composite endpoint of doubling of serum creatinine or ESKD compared to placebo (17.6% vs. 42.9%, respectively). This composite endpoint was not a priori defined [32]. These data have led to registration of octreotide LAR as treatment for ADPKD in Italy. Later, a larger study that randomized 309 ADPKD patients to the somatostatin analogue lanreotide or standard treatment (DIPAK 1) [22] found no significant effect of lanreotide on the primary outcome rate of eGFR decline compared to placebo (− 3.53 mL/min/1.73 m^2 per year vs. -3.46 mL/min/1.73 m^2, respectively), nor on worsening of kidney function (defined as a 30% eGFR decrease or start of dialysis). However, similar to earlier trials, this study also demonstrated that the rate of TKV growth was significantly reduced by a somatostatin analogue. Lastly, the LIPS study [33] also investigated lanreotide using renal function as primary outcome in 159 ADPKD patients. It was completed in 2019, but publication of the results is still awaited. A recently published systematic review concluded that somatostatin analogues as class have no significant effect on (e)GFR decline or on progression to ESKD [34]. However, the same study demonstrated that they do have an effect on change in total liver volume and possibly also kidney volume, at the

expense of side effects. It cannot be excluded that there are differences in efficacy within the class of somatostatin analogues between octreotide LAR and lanreotide, because differences in affinity for the various somatostatin receptors have been described [35]. Although somatostatin analogues do not have clear renoprotective effects, there may be a role for these agents in reducing volume-related complaints in ADPKD, especially in polycystic liver disease [36]. This topic falls beyond the scope of this review.

A more kidney-specific target for therapeutic intervention is the vasopressin 2 receptor (V2R), located on the basolateral membrane of collecting duct cells. Animal experiments showed a beneficial effect of vasopressin 2 receptor antagonists (V2RA) by limiting the generation of cAMP [37, 38]. In 2012, the landmark clinical trial with a V2RA (TEMPO 3:4 trial) was published [25]. In this multicenter trial, 1445 ADPKD patients were included with relatively early stage disease (defined as an estimated creatinine clearance of more than 60 mL/min), but who were at high risk of rapid disease progression (defined as a TKV of more than 750 mL). In these patients, the V2RA tolvaptan (90/30 mg split dose) decreased TKV growth by 49% and rate of eGFR decline on treatment by 26% (Fig. 2). After this trial, 871 patients continued in a 2-year open-label follow-up study, showing that the beneficial effect of tolvaptan on eGFR was sustained [39]. In later stage disease [26] (REPRISE trial, Fig. 2) and in a real-world setting [40], tolvaptan was also proven effective with a decrease in rate of eGFR decline of 38%. These results led to a marketing authorization for tolvaptan by, among others, the FDA and the EMA for the indication of ADPKD with a high likelihood of rapid disease progression. Despite that disease-modifying treatment is now available for clinical use, which is an important breakthrough in ADPKD, the moderate efficacy, limited tolerability (due to aquaretic events), and risk of hepatic toxicity warrant the development of additional treatment options.

4 Improving Currently Available Therapeutic Options

4.1 Overcoming Aquaretic Side Effects of Vasopressin Receptor Blockade

As stated in the Introduction, treatment with tolvaptan preserves kidney function in ADPKD, but aquaretic side effects such as polyuria, nycturia, and thirst limit its use. Many ADPKD patients opt not to be treated with tolvaptan because of these side effects, and so reducing these effects would improve the therapeutic potential of this drug. Tolvaptan blocks the vasopressin V2 receptor and thus results in

Table 1 Overview of landmark clinical trials that investigated disease-modifying drugs in autosomal dominant polycystic kidney disease (ADPKD)

Agent	Trial design	Main inclusion criteria	No. of patients	Follow-up duration	Status	Main potential adverse events	Main results
Vaptans							
Tolvaptan	TEMPO 3:4 [25] Phase 3, double-blind placebo-controlled	Age 18–50 years, CrCL ≥ 60 mL/min and TKV ≥ 750 mL	1445	36 months	Published	Aquaresis and hepatotoxicity	Reduction of TKV growth (2.8% per year for tolvaptan vs 5.5 for placebo) and eGFR decline (−2.72 mL/min/1.73m^2 per year for tolvaptan vs −3.70 for placebo) over the 3 year study period
	REPRISE [26] Phase 3, double-blind placebo-controlled	Age 18 - 65 years, eGFR 25 - 65 mL/min/1.73m^2 (eGFR 25–44 mL/min/1.73m^2 and progressive disease for patients aged 56–65 years)	1370	12 months	Published		Reduction of eGFR decline (−2.34 mL/min/1.73m^2 per year for tolvaptan vs -3.61 for placebo), but no effect on eGFR decline in patients aged > 55 years
Somatostatin analogues							
Octreotide LAR	ALADIN 1 [30] Phase 3, single-blind placebo-controlled	Age > 18 years, eGFR ≥ 40 mL/min/1.73m^2	79	36 months	Published	Cholelithiasis, acute cholecystitis and gastrointestinal side effects	Significant reduction of TKV growth after 1 year, but not after 3 years. Slower GFR decline from year 1 to 3 in the octreotide group vs placebo (-2.28 mL/min/1.73m^2 per year vs -4.32, respectively). No significant differences in GFR decline over the 3 year study period
	ALADIN 2 [31] Phase 3, double-blind placebo-controlled	Age > 18 years, eGFR 15 – 40 mL/min/1.73m^2	100	36 months	Published		Reduction of TKV growth after 1 and 3 years, but no significant differences in GFR decline between groups. Less frequent progression to a composite endpoint of doubling of serum creatinine or ESKD in the octreotide LAR group vs placebo (17.6% vs 42.9, respectively)
Lanreotide	DIPAK 1 [22] Phase 3, open label	Age 18 - 60 years, eGFR 30–60 mL/min/1.73m^2	309	30 months	Published	Hepatic cyst infection, cholelithiasis and related problems, and gastrointestinal side effects	Reduction of TKV growth (4.15% per year for lanreotide vs 5.56 for placebo), but no significant effect on eGFR decline (−3.53 ml/min/1.73m^2 per year vs −3.46 for lanreotide and placebo, respectively)
mTOR inhibitors							
Everolimus	Phase 3, double-blind, placebo-controlled [29]	eGFR > 30 mL/min/1.73m^2 and TKV > 1000 mL	433	24 months	Published	Mucositis, diarrhea, acne, increased proteinuria and reduced hematopoiesis. Angioedema when combined with ACE-inhibitors	Reduction of TKV growth after 1 year (102 mL vs 157 for everolimus and placebo, respectively). Trend towards reduction of TKV growth after 2 years (230 mL for everolimus vs 301 for placebo, p=0.06). No significant differences in eGFR decline between groups
Sirolimus	Phase 3, open label [28]	Age 18–40 years, eGFR ≥ 70 mL/min/1.73m^2	100	18 months	Published	Mucositis, diarrhea, acne and peripheral edema	No significant effects on TKV growth (7.8% per year for sirolimus vs 6.8 for placebo). No differences in eGFR decline between groups. Higher urinary excretion rates in the sirolimus group compared to placebo

CrCL creatinine clearance, *eGFR* estimated glomerular filtration rate, *LAR* long-acting repeatable, *mTOR* mammalian target of rapamycin, *TKV* total kidney volume

△ Adis

a state that resembles diabetes insipidus. It therefore seems reasonable to apply strategies during tolvaptan use that have been proven to limit aquaresis in other forms of diabetes insipidus. The first strategy could be to lower the excretion of urinary osmoles by dietary interventions [41]. Since tolvaptan impairs the urinary concentrating capacity, osmolar excretion drives the amount of aquaresis. A decrease in urinary osmole excretion will correspondingly result in a decrease in urine volume. Whether this can be achieved by limiting protein as well as by limiting salt intake is the subject of clinical investigation [42]. Experimental evidence suggests that co-prescription with metformin also reduces polyuria during tolvaptan treatment [43], possibly by a vasopressin-independent upregulation of AQP-2 channels in the collecting duct [44]. However, in a small-scale cross-over study, the tolerability of metformin appeared less than that of hydrochlorothiazide due to gastrointestinal side effects [45], and consequently, metformin did not improve quality of life [43]. A third method might be to co-prescribe a thiazide diuretic, such as hydrochlorothiazide. Although seemingly paradoxical, co-treatment with a thiazide diuretic may lead to (considerably) less 24-h urine production. The mechanism is not fully understood, but it is assumed that blockage of the NCC channel with a thiazide diuretic leads to a state of mild volume depletion. The compensatory increase in salt and water reabsorption in the proximal tubule then results in a decreased urinary volume. In two small-scale clinical trials, this strategy resulted in a significant decrease in urinary volume and an improved quality of life in patients on tolvaptan [43, 46]. This was corroborated in an experimental study that suggested that co-treatment with a thiazide diuretic may also increase the renoprotective efficacy of tolvaptan [43]. Whether such a strategy also has longer-term effects in human ADPKD is going to be investigated in a large-scale clinical trial that is due to start in 2022 [24].

4.2 Overcoming Systemic Adverse Events; Targeted Treatment

Since molecular targets that are involved in cyst growth are also involved in other important biological processes in the body (such as cellular growth, proliferation, and repair), targeting these pathways may cause important systemic adverse events. In line, several potential therapies in ADPKD were very effective in animal models, but clinical studies were disappointing because systemic adverse events and toxicity limited adequate dosing. Given that chronic treatment is necessary for ADPKD (in contrast to, e.g., cancer treatment), adverse events should be kept to a minimum.

As mentioned above, an example of the inability to reach therapeutic dosage due to adverse effects is mTOR inhibition. For mTOR inhibition, clear attenuation of renal cystic disease was shown in several rodent models [47]. However, two clinical trials with mTOR inhibitors produced disappointing results, probably because side effects such as mucositis and diarrhea led to suboptimal dosing [28, 29]. Tissue targeting of these drugs to renal cysts, thereby minimizing drug exposition in extrarenal tissues, may be a potential way around this problem.

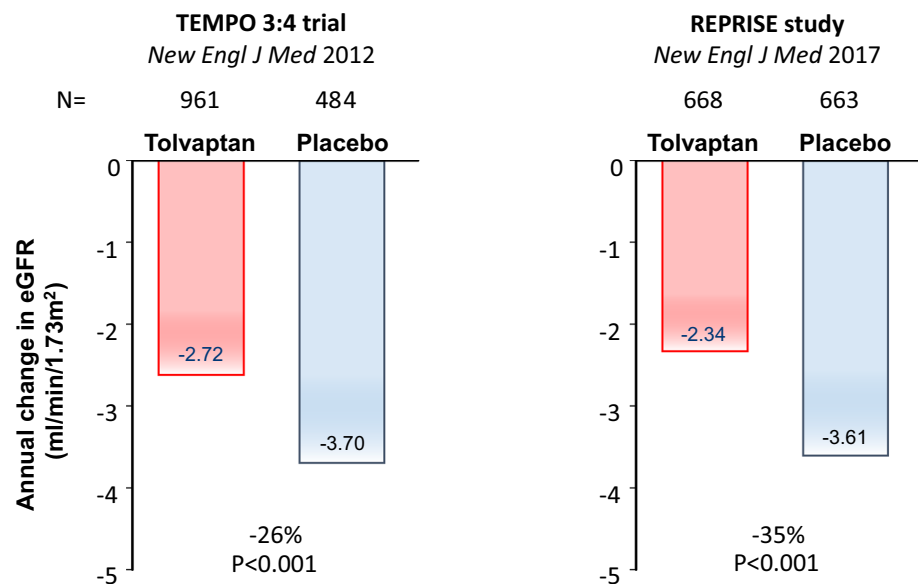### 4.2.1 Targeting Drugs to Renal Cysts Via the Folate Receptor

In cancer, many tumors express the folate receptor-α (FRα). Using this receptor, folate-conjugated compounds can be taken up by receptor-mediated endocytosis [48]. Since cyst-lining cells also express the folate receptor-α (FRα), this enables the delivery of drugs specifically to these cells [49]. Folate-conjugated sirolimus (an mTOR inhibitor) is an engineered compound with a cleavable linker that allows the intracellular release of sirolimus in cyst-lining cells. An experimental study showed that this mechanism works in mice. The renoprotective effect of folate-conjugated sirolimus was comparable to that of unconjugated sirolimus, whereas systemic effects as weight loss and cell cycling in the thymus were absent [50]. This therapeutic strategy may also be used for other small molecules that have shown promising results in experimental studies, but whose therapeutic effect may be limited by adverse events, for example epidermal growth factor receptor (EGFR) inhibition (as described in section 5.8, Other Agents).

4.2.2 Targeting Drugs to Renal Cysts Via the Polymeric Immunoglobin Receptor

Drugs may also be targeted to renal cysts by coupling to monoclonal antibodies (mAb) that bind receptors on the basolateral membrane of the renal tubular cell, after which the drug:mAb complex is internalized and the drug is released. By reducing the drug exposition of extrarenal tissues, fewer off-target adverse effects are expected. A major obstacle, however, is that most available monoclonal antibodies are of the IgG type, which are not capable of crossing the epithelial barrier of renal cysts [51]. Some drug targets, like EGFR, are localized on the apical membrane of renal tubular cells in ADPKD [52]. In these cases, even though an IgG-bound drug may target a component of the basolateral membrane of renal tubular cells, the drug would still have to be transported through the cytoplasm and across the apical cell membrane to exert an effect.

It was recently found that the polymeric immunoglobin receptor (pIgR) is highly expressed on the basolateral membrane of cyst-lining cells in ADPKD [51]. This

Fig. 2 Treatment effect of tolvaptan on annual rate of estimated glomerular filtration rate (eGFR) decline in the TEMPO 3:4 and REPRISE trials [25, 26]. Tolvaptan reduced the annual eGFR decline by 26% and 35% in the TEMPO 3:4 and REPRISE studies, respectively

TEMPO 3:4 trial
New Engl J Med 2012

N=   961   484
Tolvaptan   Placebo

Annual change in eGFR (ml/min/1.73m²)

-2.72
-3.70

-26%
P<0.001

REPRISE study
New Engl J Med 2017

668   663
Tolvaptan   Placebo

-2.34
-3.61

-35%
P<0.001

transmembrane protein is capable of binding polymeric immunoglobulins (pIg) of the IgA and IgM subtypes. The pIgR:pIg complex is then transcytosed through the cytoplasm to the apical membrane, where proteolytic cleavage releases the immunoglobulin into the cyst lumen (in complex with an extracellular portion of the pIgR) [51]. The same study demonstrated that in a murine ADPKD model, pIgR-mediated transport of dimeric IgA (dIgA) is unilateral and leads to an accumulation of dIgA in the renal cyst lumen. This opens up the idea of reformatting antagonistic monoclonal antibodies against growth factors or receptors implicated in ADPKD to the dIgA subtype for delivery to the cyst lumen by this mechanism. An example is the EGF receptor. Although EGFR antibodies that are currently in clinical use are of the IgG isotype, anti-EGFR antibodies of the IgA isotype have previously been engineered for use in oncological immunotherapy [53]. It is important to note that pIgR is also expressed in other epithelial tissues, like bronchial and gastrointestinal mucosa [54]. While these tissues may have less potential for drug accumulation than renal cysts because of their secretory nature, they may still be exposed to the drug to some extent which could lead to adverse events.

5 Drugs Under Investigation in Clinical Trials

The main emerging renoprotective therapies that are currently being investigated in clinical trials are discussed in detail below. Figure 3 gives a simplified overview of potential treatment targets in a renal tubular cell and Table 2 summarizes the ongoing or recently completed clinical trials that have been performed in ADPKD.

5.1 Lixivaptan

Tolvaptan potentially causes severe hepatotoxic reactions, and carries a Black Box Warning in the USA [55] and EU [56] that cautions against the risk of liver injury. The mechanism that causes hepatocellular damage is still unknown. Regular monitoring of liver function tests is therefore warranted; monthly during the first 18 months of treatment and every 3 months thereafter. Clear decision rules have been defined on when to temporarily withhold or stop treatment in case of liver function test abnormalities [55, 56]. Severe hepatotoxic reactions to tolvaptan are extremely rare when such precautions are taken. Lixivaptan is an alternative V2RA that is hypothesized to carry less risk of hepatocellular toxicity. This is based upon quantitative systems toxicology modeling, that correctly predicted hepatotoxicity of tolvaptan [57]. Like tolvaptan, lixivaptan prevents the insertion of aquaporin channels into the collecting duct by competitively binding and antagonizing V2 receptors, leading to decreased cAMP production and subsequently, reduced cyst proliferation. It also leads to increased solute-free water excretion. Lixivaptan has a higher affinity for the V2 receptor than other VRAs, and is metabolized in the liver with a half-life of 7–10 h [58]. It was investigated for treatment of hyponatremia in congestive heart failure [59, 60] and liver cirrhosis [61], where lixivaptan was effective in increasing serum sodium concentrations. In these studies, significant hepatotoxic reactions in response to lixivaptan did not occur.

At the end of 2021, a large phase 3 placebo-controlled, randomized clinical trial (ACTION) was started to investigate the efficacy and safety of lixivaptan in participants with ADPKD [62]. This trial is designed to demonstrate the efficacy of lixivaptan in slowing the decline in renal

function as measured by the difference in eGFR between the lixivaptan-treated and placebo-treated participants during 1 year, followed by an open-label extension period. The primary endpoint is the annualized change in eGFR from baseline to follow-up. Secondary endpoints are, amongst others, hepatocellular toxicity (defined as an increase of serum ALT levels >3 x ULN) and changes in TKV. The design of this trial strongly resembles that of the landmark REPRISE study [26], which has proven the efficacy of tolvaptan in later-stage disease. In view of their similar effects on hyponatremia and the high affinity of lixivaptan for the V2 receptor, it is expected that lixivaptan will have a similar renoprotective efficacy to tolvaptan. In that respect, it may be problematic to include patients in this study where they might receive a placebo, when tolvaptan is available for clinical use. Perhaps it is more appropriate to first demonstrate the safety of lixivaptan in patients with contraindications to treatment with tolvaptan due to hepatocellular toxicity. A phase 3, open-label study (ALERT) will administer lixivaptan to 50 patients with previous hepatotoxic reactions to tolvaptan and follow them for 12 months [63]. The primary endpoint is hepatic safety and the estimated study completion date is November 2022.

5.2 Glucosylceramide Synthase (GCS) Inhibitors

Another class of drugs that are momentarily under investigation in clinical trials as renoprotective agents in ADPKD are glucosylceramide synthase (GCS) inhibitors, among which is venglustat. These drugs decrease the synthesis of glucosylceramide (GL-1), a central building block for more complex glycosphingolipids (GSLs). GSLs are part of the cell membrane and thus necessary for normal physiological processes. However, in some diseases including lysosomal storage diseases (such as Fabry and Gauchier disease), an increased amount of GL-1 and other GSLs is found. Surprisingly, and not predicted based on knowledge of the pathophysiology of the disease, murine and human ADPKD were found to be also accompanied by increased GCS activity, leading to a pathogenic accumulation of GSLs such as GL-1, lactosylceramide (GL-2), and GM3 [64, 65]. Subsequently, it was shown that treatment with a GCS inhibitor significantly reduced cyst growth and preserved renal function in three different polycystic kidney disease (PKD) animal models [66]. In October 2018, the STAGED-PKD study [23] was therefore initiated to examine the effect of venglustat in ADPKD patients at risk for progressive disease based on Mayo classification (class 1C-E) and renal function (eGFR 30–90 mL/min/1.73 m^2). Unfortunately, this study was terminated prematurely in

August 2021, after an interim analysis showed lack of efficacy. Publication of the results of this trial is awaited.

Currently, another GCS inhibitor, AL01211, is being investigated in a phase 1 clinical study [67]. This study is currently recruiting and aims to include 80 healthy subjects and 18 ADPKD patients. The estimated study completion date is June 2022.

5.3 Nuclear Factor Erythroid-2 Related Factor 2 (Nrf2) Activators

Oxidative stress has emerged as a significant contributor to disease progression in ADPKD [68]. Nuclear factor erythroid-2 related factor 2 (Nrf2) is an important transcription factor for regulating the defensive response against oxidative stress [69]. Under normal circumstances, Nrf2 is bound to one of three ubiquitin ligase complexes, most importantly keap1-cullin 3-Ring box 1 (Keap1-CUL3-RBX1) [70], and is consequently targeted for rapid ubiquitin-proteasomal degradation. Oxidative stress induces conformational changes in the Keap1 molecule, releasing Nrf2 from the Keap1-CUL3-RBX1 complex and allowing it to translocate to the nucleus. Here, Nrf2 binds to the antioxidant response element to induce the transcription of numerous target genes and thereby reduce oxidative stress, among other cytoprotective effects [71]. In an orthologous ADPKD mouse model, Nrf2 deletion increased ROS generation and promoted cyst growth, while pharmacological Nrf2 induction reduced ROS production and cystogenesis [68].

Bardoxolone is a potent activator of Nrf2 [72, 73] that was originally developed as an antineoplastic drug. In addition to the activation of Nrf2, bardoxolone inhibits the nuclear factor κB (NF-κB) inflammatory pathway [74]. Bardoxolone was found to have renoprotective effects in a phase 1 clinical trial that included patients with advanced solid tumors and lymphomas [75] and was then investigated in diabetic kidney disease (DKD) [76, 77]. The BEAM trial was a randomized controlled trial involving 227 patients with type 2 diabetes and advanced chronic kidney disease (eGFR 20–45 mL/min/1.73 m^2) who were assigned to placebo or varying doses of bardoxolone methyl [78]. At 52 weeks, treatment with bardoxolone was associated with an increased eGFR compared to placebo in all dose groups. The most common adverse event in this study were muscle spasms. After this pilot study, a large-scale follow-up study (BEACON trial) was designed to test the effect of bardoxolone in 2,185 type 2 diabetics with stage 4 CKD (eGFR 15–29 mL/min/1.73 m^2). This study also found a significant increase in eGFR in bardoxolone treated patients. In addition, an increase in urinary albumin to creatinine ratio (ACR) was reported, which may point towards drug-induced glomerular hyperfiltration. However, the study was discontinued because of higher rates
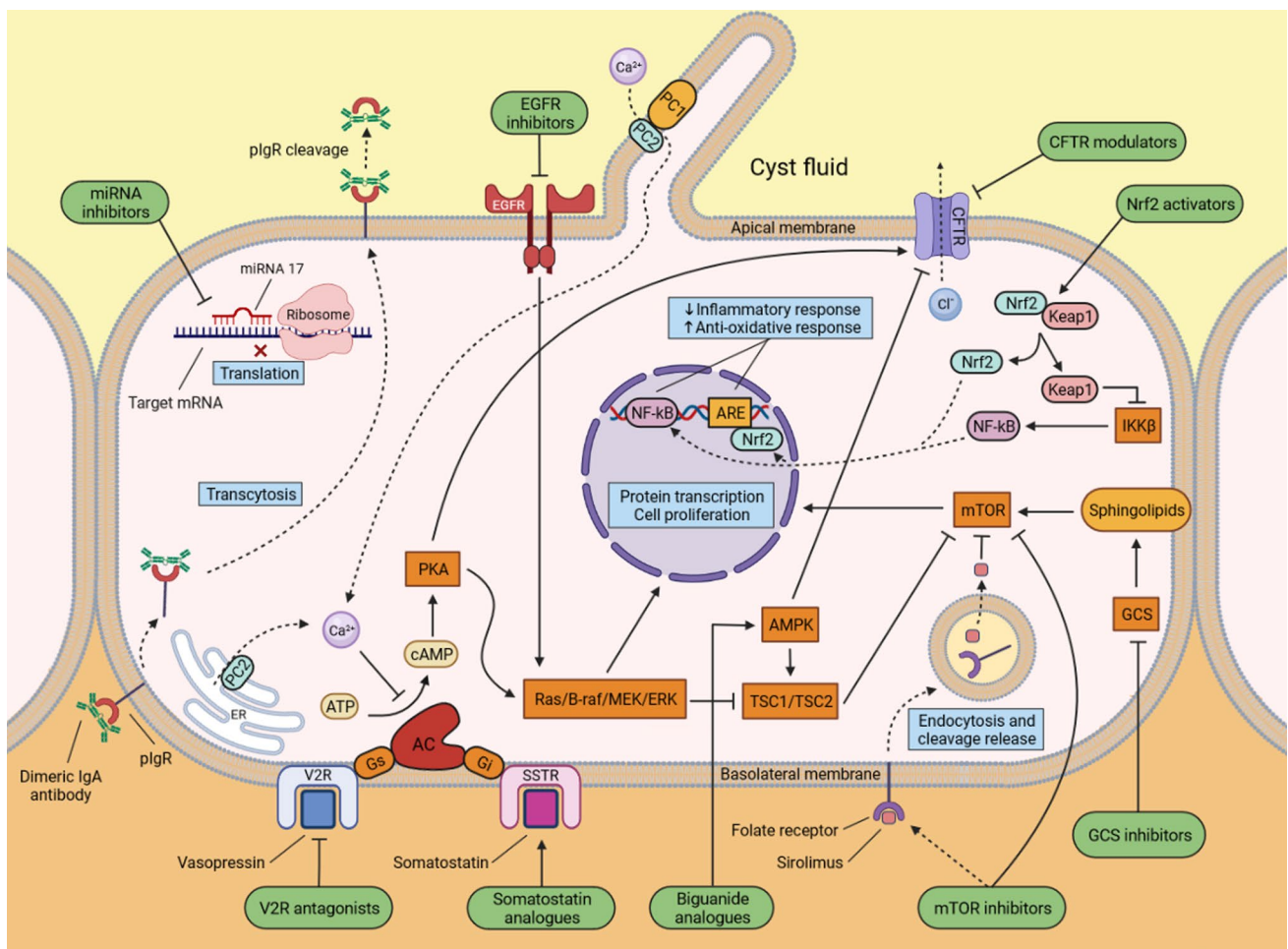
Fig. 3 Illustration of the principal mechanisms of autosomal dominant polycystic kidney disease (ADPKD) pathogenesis and main targets of potential treatments. Dysfunction of polycystin 1 and 2 leads to abnormal ciliary function and a decrease in the intracellular calcium concentration, resulting in increased cAMP generation and mTOR activity which subsequently promote protein transcription and cell proliferation. Current and potential treatment options are depicted in green. *AC* adenylyl cyclase, *ARE* antioxidant response element, *ATP* adenosine triphosphate, *AMPK* 5' AMP-activated protein kinase, *B-raf* serine/threonine-protein kinase B-Raf, *cAMP* cyclic adenosine monophosphate, *CFTR* cystic fibrosis transmembrane conductance regulator, *EGFR* epidermal growth factor receptor, *ER* endoplasmatic reticulum, *ERK* extracellular signal-regulated kinase, *GCS* glucosylceramide synthase, *Gi* inhibitory G protein of adenylyl cyclase, *Gs* stimulatory G protein of adenylyl cyclase, *IKKβ* I-kappa-B kinase unit beta, *Keap1* Kelch-like ECH-associated protein 1, *MEK* mitogen-activated protein kinase kinase, *miRNA 17* micro RNA 17, *mTOR* mammalian target of rapamycin, *NF-κB* nuclear factor kappa B, *Nrf2* nuclear factor erythroid 2-related factor 2, *PC1* polycystin 1, *PC2* polycystin 2, *PKA* protein kinase A, *pIgR* polymeric immunoglobulin receptor, *SSTR* somatostatin receptor, *TSC1/TSC2* tuberous sclerosis complex subunit 1/2, *V2R* vasopressin receptor 2

of cardiovascular events and heart failure in the bardoxolone group [79]. Post hoc analyses showed that elevated B-type natriuretic peptide and previous hospitalizations for heart failure were predictive of these adverse events [80]. In a more recent trial that also studied the effects of bardoxolone in DKD, and that excluded patients at risk for heart failure, no episodes of heart failure were observed [81]. These data suggest that bardoxolone might be beneficial in progressive kidney diseases characterized by oxidative stress and a low risk of heart failure, such as ADPKD. However, the increase in albuminuria in bardoxolone-treated patients, which may reflect drug-induced glomerular hyperfiltration, could be detrimental to renal function during long-term treatment.

Unpublished data from the PHOENIX study, an open label phase 2 study, suggested an improvement in kidney function in 31 ADPKD patients treated with bardoxolone (mean eGFR improvement of 6.6 mL/min/1.73 m^2 at Week 4 (p < 0.0001), increasing to 12.0 mL/min/1.73 m^2 at Week 12 (p < 0.0001) from a mean baseline eGFR of 47.7 mL/min/1.73 m^2. Data on albuminuria from this study are not available. A follow-up phase 3 placebo-controlled study (FALCON) [82] is currently recruiting to investigate the

Table 2 Overview of the most important ongoing or recently completed clinical trials investigating disease-modifying drugs in ADPKD

Agent	Trial design	Main inclusion criteria	No. of patients	Follow-up duration (mo)	Status	Main potential adverse events	Primary outcome/main results
Vaptans							
Lixivaptan	ALERT [63] Phase 3, open label	Age 18–65 years, eGFR ≥ 20 mL/min/1.73 m², contra-indication to treatment with tolvaptan due to hepatocellular toxicity	50	16.8	Active, recruiting	Aquaresis	Hepatic safety (indicated by serum ALT levels)
	ACTION [62] Phase 3, double-blind placebo-controlled, followed by 1 year open label phase	Age 18–60 years, eGFR 25–90 mL/min/1.73m², Mayo class 1C, 1D or 1E	1200	24	Active, recruiting		Annualized change in eGFR during the first study year (placebo-controlled phase)
Somatostatin analogues							
Lanreotide	LIPS [33] Phase 3, double-blind, placebo-controlled	Age > 18 years, mGFR 30 – 89 mL/min/1.73m²	159	36	Completed, unpublished	Hepatic cyst infection, cholelithiasis and related problems, and gastrointestinal side effects	Changes in measured GFR
Octreotide LAR plus tolvaptan vs tolvaptan	TOOL [170] Phase 2, double-blind, placebo-controlled	Age > 18 years, mGFR > 80 mL/min/1.73m² and stable renal function, TKV 1000–2000 mL	20	4	Active, not recruiting	Cholelithiasis, acute cholecystitis and gastrointestinal side effects	Changes in measured GFR
GCS inhibitors							
Venglustat	STAGED-PKD [23] Phase 2-3, double-blind placebo-controlled	Age 18–55 years, eGFR > 30 mL/min/1.73m² and < 90 mL/min/1.73m², Mayo class 1C, 1D or 1E	478	26	Terminated, unpublished	Gastrointestinal side effects, possibly also ocular lens degeneration and depression	Terminated for futility based on interim analyses. Primary outcomes were changes in TKV, the results are not yet available
AL01211	Phase 1, double-blind placebo-controlled [67]	Age 18–55 years, eGFR 30–89 mL/min/1.73m² for ADPKD patients	98 subjects (18 ADPKD patients)	3	Active, recruiting	Unknown	Safety and tolerability (based on incidence of (serious) adverse events)
Nrf2 activators							
Bardoxolone	FALCON [82] Phase 3, double-blind placebo-controlled	Age 18–70 years, eGFR 30–90 or 30–44 mL/min/1.73m² depending on age. Patients with eGFR ≥ 60 mL/min/1.73m² or age ≥ 56 years must have progressive disease (eGFR decline of ≥ 2.0 mL/min/1.73m² per year). No evidence of cardiac disease	550	24	Active, recruiting	Congestive heart failure and possibly tubuloglomerular damage secondary to glomerular hyperfiltration	Changes in eGFR between baseline and week 108 (off-treatment), and safety

Table 2 (continued)

Agent	Trial design	Main inclusion criteria	No. of patients	Follow-up duration (mo)	Status	Main potential adverse events	Primary outcome/main results
CFTR modulators							
GLPG2737	Phase 2, double-blind, placebo-controlled followed by 1 year open label phase [96]	Age 18–50 years, eGFR 30–90 or 30–60 mL/min/1.73m^2 depending on age, TKV >750 mL and Mayo class 1C, 1D or 1E	66	24	Active, not recruiting	Possibly nasopharyngitis, headache, pulmonary and gastrointestinal side effects	Changes in htTKV and safety
Biguanide analogues							
Metformin	Phase 2, double-blind, placebo-controlled [45]	Age 30–60 years, eGFR 50–80 mL/min/1.73m^2, non-diabetic	51	12	Published	Gastrointestinal side effects, vitamin B12 deficiency and lactic acidosis	82% of patients tolerated a metformin dose of ≥ 1000 mg/day. No significant differences in changes of htTKV or eGFR between metformin and placebo groups (exploratory outcomes)
	TAME [110] Phase 2, double-blind, placebo-controlled	Age 18–60 years, eGFR > 50 mL/min/1.73m^2, non-diabetic	97	26	Published		67% of metformin treated patients tolerated the target dose of 2000mg/day. No significant differences in changes of htTKV or eGFR between metformin and placebo groups (exploratory outcomes)
Metformin extended release	IMPEDE-PKD [111] Phase 3, double-blind, placebo-controlled	Age 18–70 years, eGFR 45–90 mL/min/1.73m^2 and (risk of) rapidly progressive disease (based on volumetric criteria, PROPKD score or eGFR decline), non-diabetic	1164	24	Active, not yet recruiting		Changes in eGFR
miRNA inhibitors							
RGLS4326	Phase 1, open label [123]	Age 18–70 years, eGFR 30–90 mL/min/1.73m^2, Mayo class 1C, 1D or 1E	19	2.3	Completed, unpublished	Unknown	Changes in polycystin 1 and -2 levels in urinary exosomes
Other agents							
Pravastatin	Phase 4, double-blind, placebo-controlled [148]	Age 25–60 years, eGFR ≥ 60 mL/min/1.73m^2, TKV > 500 mL	200	24	Active, recruiting	Muscle pain, headache, gastrointestinal side effects	Changes in TKV

△ Adis

Table 2 (continued)

Agent	Trial design	Main inclusion criteria	No. of patients	Follow-up duration (mo)	Status	Main potential adverse events	Primary outcome/main results
	Phase 3, double-blind, placebo-controlled [171]	Age 8–22 years, eGFR ≥ 80 mL/min/1.73m²	110	36	Completed, published		Reduced increase of several proinflammatory and oxidative stress markers in pravastatin treated patients compared to placebo
Pravastatin plus sodium citrate	ADPKD-SAT [149] Phase 2, open label	Age > 18 years, eGFR ≥ 30 mL/min/1.73m² and evidence of metabolic acidosis	30	12	Active, recruiting		Changes in kidney function, liver function, blood pressure and incidence of muscle tenderness/rhabdomyolysis
Pioglitazone	PIOPKD [151] Phase 1b, double-blind, placebo-controlled	Age 18–55 years, eGFR ≥ 50 mL/min/1.73m² and (risk of) rapidly progressive disease (based on volumetric criteria), non-diabetic	18	24	Completed, published	Hypoglycemia	Low-dose pioglitazone appeared safe. No effect on TKV or eGFR
Tesevatinib	Phase 1-2, open label [172]	Age 18–62 years, eGFR ≥ 35 mL/1.73m², htTKV ≥ 1000 mL	74	24	Completed, unpublished	QT-prolongation, diarrhea and acne	Safety, pharmacokinetics, maximum tolerated dose and changes in eGFR
	Phase 2, double-blind, placebo-controlled [152]	Age 18–60 years, eGFR 25–90 mL/min/1.73m², htTKV ≥ 500 mL, ≥ 750 mL or ≥ 900 mL depending on age	80	24	Active, not recruiting		Changes in htTKV
Curcumin	Phase 4, double-blind, placebo-controlled [164]	Age 6–25 years, eGFR > 80 mL/min/1.73m²	68	12	Completed, published	Nausea and diarrhea (at high doses)	No differences between surrogate markers of vascular endothelial dysfunction and arterial stiffness in curcumin treated patients vs placebo. No significant differences in htTKV or eGFR (exploratory outcomes)

ADPKD autosomal dominant polycystic kidney disease, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *mo* months, *mGFR* measured GFR, *TKV* total kidney volume, *htTKV* height-adjusted TKV

safety, tolerability, and efficacy of bardoxolone in ADPKD patients without evidence of cardiac disease. The primary efficacy endpoint is the change in eGFR from baseline to 4 weeks after withdrawal in bardoxolone versus placebo-treated patients. This study aims to enroll 550 patients with an eGFR of 30–90 mL/min/1.73 m^2 for patients 18–55 years of age, or 30–45 mL/min/1.73 m^2 for patients aged 55–70 years. In addition, when the eGFR is between 60 and 90 mL/min/1.73 m^2 or when age is between 55 and 70 years, patients must have evidence of ADPKD progression, i.e., a historical annual rate of eGFR decline ≥ 2.0 mL/min/1.73 m^2. Given the average eGFR decline of approximately 3.5 mL/min/1.73 m^2 per year in placebo-treated patients from previous ADPKD trials [25, 26], it is uncertain whether these inclusion criteria sufficiently select patients at risk for rapid disease progression. As such, the effects of bardoxolone in this study may be obscured. Additionally, as mentioned above, the increase of albuminuria in previous studies possibly indicates glomerular hyperfiltration. In view of the potential harmful effects of long-standing glomerular hyperfiltration, this study will address the question whether long-term treatment with bardoxolone is safe and effective. The estimated completion date of this study is December 2023.

5.4 Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators

Transepithelial chloride secretion is a key pathogenetic mechanism behind cystogenesis and is mediated by cystic fibrosis transmembrane conductance regulator (CFTR). This Cl- channel is primarily located in the apical membrane of cyst lining cells and stimulates the secretion of chloride ions into cyst fluid [83, 84]. The resulting negative ion gradient is followed by transepithelial movement of Na+ ions and subsequently by water molecules (respectively termed "electric" and "osmotic coupling"), leading to cyst expansion [85]. The activity of CFTR is in part regulated by protein kinase A (PKA) and AMP-activated protein kinase (AMPK), and therefore depends on intracellular cAMP levels [86, 87]. The observation that some individuals with ADPKD and concurrent homozygous CFTR mutations (leading to cystic fibrosis; CF) exhibit an attenuated ADPKD phenotype may suggest a role of CFTR in cystogenesis [88, 89]. However, another similar study did not find such an association [90].

It was subsequently shown that two CFTR inhibitors of the thiazolidinone and glycine hydrazide groups slow cyst formation in a murine embryonic kidney cyst model. In the same study, treatment of kidney-specific *PKD1*-knockout mice with either compound reduced cyst growth and preserved renal function [91]. VX-809 (Lumacaftor), one of the available CFTR modulators originally designed to treat CF, restores the folding and cellular trafficking of mutant CFTR proteins [92]. Treatment of *PKD1*-knockout mice

with VX-809 induced the localization of CFTR proteins to the basolateral membrane of cyst lining cells. In addition, the translocation of Na+/H+ exchanger 3 and epithelial sodium channels to the apical membrane were increased. Together, these effects were hypothesized to promote net resorption of cyst fluid and thereby reduce cyst growth [93, 94]. A follow-up study by the same authors produced similar results on cyst growth, while also preserving renal function in VX-809 treated *PKD1*RC/RC mice [95].

Given these promising results, a phase 2, placebo-controlled, randomized, controlled trial (RCT) was started to investigate the safety and tolerability of the CFTR modulator GLPG2737 in 66 ADPKD patients at risk for rapidly progressive disease [96]. The treatment duration is 12 months, followed by an optional open label extension period of another 12 months. The estimated study completion date is February 2024. Seeing as this drug influences CFTR activity, which is altered in CF, one of the issues to be addressed will be the adverse event profile given the possibility of pulmonary and gastrointestinal side effects (corresponding to the clinical features of CF).

5.5 Biguanide Analogues

The biguanide analogue metformin is a well-known first line treatment for type 2 diabetes mellitus. It also has beneficial effects in other diseases such as polycystic ovary syndrome and non-alcoholic fatty liver disease [97, 98]. Metformin has been prescribed for decades and generally has a good safety profile, although there are dose-dependent gastrointestinal adverse events, such as nausea, abdominal pain and diarrhea. Moreover, lactic acidosis is a significant potential risk, particularly in patients with impaired renal function [99].

Abnormal polycystin signaling in renal tubular PKD cells is accompanied with a metabolic shift to glycolysis (similar to the Warburg effect in cancer cells) and excessive ATP production [100]. AMPK serves as a cellular energy-sensing molecule that inhibits mTOR signaling and CFTR activity during energy depletion [87, 101, 102]. The enhanced metabolic rate in PKD cells inhibits AMP-activated protein kinase (AMPK), thus leading to increased mTOR signaling and CFTR activity, which respectively stimulate the proliferative and secretory aspects of cyst formation [103]. Metformin activates AMPK and could reduce ADPKD disease progression through the abovementioned mechanisms [103].

Several preclinical in vivo studies have found beneficial effects of metformin on ADPKD disease parameters such as cystic index [103–106], with some also describing an improved renal function [105, 106]. However, a recently conducted study demonstrated no effect on cystic index or renal function in a murine ADPKD model [107], while another study reported a paradoxical increase in cystic index and worsened renal function in metformin-treated mice [108].

These discrepant results could be explained by heterogeneity in terms of animal models, the timing of treatment relative to cyst formation, the method of metformin administration (some studies delivered metformin by intraperitoneal injection, thereby circumventing first pass effects) and treatment duration. Of note, some authors drew attention to the dose of metformin that was given in the various experimental models, with only models in which high dosages were given reaching positive results [109]. By extrapolating these data, they reasoned that metformin should be given in a dose of at least 2000 mg/day to patients with ADPKD to achieve beneficial effects.

To date, two placebo-controlled small-scale phase 2 trials have been performed in non-diabetic ADPKD patients with varying degrees of renal insufficiency [45, 110]. Although metformin treatment appeared to be safe in these patients, limited tolerability due to gastrointestinal side effects could impact its therapeutic potential. For example, Brosnahan et al. reported that only 50% of 51 metformin-treated patients tolerated the target dose of 2000 mg/day [45]. Exploratory analyses showed no effects on height adjusted TKV (htTKV) growth or renal function decline, although these studies were not powered to detect such differences and they were not enriched for inclusion of patients with rapidly progressive disease [45, 110]. Additional studies are therefore needed.

Recently, a phase 3 study to investigate the effect of metformin on disease progression has been announced (IMPEDE-PKD) [111]. This placebo-controlled RCT will include 1164 ADPKD patients with CKD stages 2–3A (eGFR 45–90 mL/min/1.73 m^2) and risk of rapid disease progression (based on kidney volume or previous rate of renal function decline), for a total treatment duration of 24 months. The primary endpoint will be change in eGFR, and metformin will be dosed at 1000–2000 mg/day. The use of an extended-release metformin formulation in this study could enhance its tolerability and thus prevent the need to down-titrate, consequently optimizing the potential therapeutic effect.

Of note, the gastrointestinal side effects of metformin could influence dietary patterns. Salt intake has been shown to be associated with the rate of kidney function decline in ADPKD [112], possibly because a higher intake of osmoles increases vasopressin secretion and, subsequently, cAMP production in renal tubular cells. We therefore suggest monitoring dietary osmole intake by measuring sodium and protein intake in interventional studies that investigate metformin to exclude any confounding effects.

5.6 miRNA Inhibitors

Micro RNA inhibitors or anti-micro RNAs (anti-MiRs) are a new class of drugs that are being investigated for use in ADPKD. Micro RNAs (miRNAs or miRs) are short, noncoding RNA fragments that function as sequence-specific, posttranscriptional inhibitors of gene expression. The binding of miRNAs to target mRNA transcripts results in translational repression and, ultimately, to degradation of the targeted mRNA sequence [113]. Anti-MiRs are modified nucleotides designed to sterically hinder miRNAs, thus leading to de-repression of the target mRNA sequence and increased expression of encoded proteins [114]. Multiple miRNAs are abnormally expressed in ADPKD, and assumed to be causally related to the rate of disease progression [115]. Currently, miR-17 is the only miRNA that is targeted in clinical trials in ADPKD. We will therefore briefly discuss the role of miR-17 in ADPKD pathogenesis. Other miRNAs and their possible role in ADPKD are reviewed elsewhere [115].

miR-17 is part of a polycistronic cluster (miR-17~92) that produces six individual miRNAs (miR-17, -18, -19a, -20a, -19b-1 and -92-1) [116]. In both murine and human ADPKD, the miR-17~92 cluster is vastly overexpressed and genetic deletion of the cluster mitigates disease progression in ADPKD mouse models [117, 118]. Transgenic upregulation of c-Myc, a transcription factor that controls transcription of miR-17~92, promotes cyst formation in murine kidney tubules [119]. Additionally, cyst growth is reduced when *PKD1*-knockout mice are treated with anti-miR-17 [120], which supports the notion that miR-17 is an important driver of disease progression in ADPKD.

Numerous mRNA transcripts are subject to miR-17 binding and therefore, miR-17 controls the expression of many different target genes (both directly and indirectly). This includes major regulatory genes involved in proliferative signaling pathways such as PPARA and mTOR119, which could explain the effect of miR-17 on cyst growth and disease progression. In addition, miR-17 seems capable of directly binding and repressing the mRNA transcripts of *PKD1*, *PKD2* and *HNF-1β* [118, 121]. Conversely, anti-miR-17 treatment increases *PKD1* and *PKD2* expression [122]. This is especially important in case of hypomorphic mutations, where cyst growth is promoted because *PKD1* and *PKD2* activity falls below a critical threshold. Therefore, the effects of anti-miR-17 treatment are likely mediated through several signaling pathways and possibly also by a direct effect on *PKD1* and *PKD2* expression.

RGLS4326 and RGLS8429 were developed as anti-miR-17 oligonucleotides that preferentially target the kidney. RGLS4326 inhibits cyst growth in multiple PKD mouse models and human in vitro ADPKD models [122]. A dose-escalating phase 1b study was recently performed to assess the short-term safety and tolerability of RGLS4326 [123], but its results are not yet available. Recently, a phase 1b clinical study with RGLS8429 was also announced. Although anti-miR-17 treatment is an intriguing potential ADPKD

treatment option, it is currently unclear whether long-term treatment is safe, especially in view of its effects on proliferative signaling pathways that are ubiquitous throughout the body.

5.7 Uric Acid-Lowering Therapy

Both in healthy subjects and in patients with various forms of chronic kidney disease, high serum uric acid concentrations have been associated with the development and progression of renal disease [124–128]. In ADPKD, several studies also point towards an association between high serum uric acid and disease progression [129, 130], although this association was not evident in other studies [131, 132]. In addition, hyperuricemic ADPKD patients with preserved renal function seem to display higher rates of endothelial dysfunction [133], which is an early indicator of cardiovascular disease [134].

Since uric acid is primarily excreted by the kidney [135], a loss of glomerular filtration rate is expected to cause a rise of serum uric acid levels. Hyperuricemia may therefore simply be viewed as a marker of impaired renal function in patients with chronic kidney disease. Nevertheless, an increasing body of preclinical evidence suggests a causal role of uric acid in the development of renal dysfunction through several mechanisms, including the induction of oxidative stress, proliferation of vascular smooth muscle cells and promotion of epithelial-to-mesenchymal transition in renal tubular cells (as reviewed elsewhere [136]). Such effects could also influence renal outcomes in ADPKD. Despite reports of an increased prevalence of renal cysts in patients with gout, in type 2 diabetics with hyperuricemia and in some hereditary syndromes associated with hyperuricemia [137–139], experimental evidence of the ability of uric acid to directly promote renal cyst formation is lacking.

Xanthine oxidase inhibitors (e.g., allopurinol, oxypurinol, febuxostat) are the preferred treatment for hyperuricemia because of their effectiveness and generally favorable safety profile, even in patients with CKD [140, 141]. Uricosuric agents such as benzbromarone are also available to reduce serum uric acid levels. The effect of uric acid-lowering therapy on disease progression in ADPKD was retrospectively analyzed in two studies. Han et al. describe that, while hyperuricemia was not an independent predictor of renal function decline in their cohort, the initiation of uric acid-lowering therapy appeared to mitigate annual eGFR decline in 53 ADPKD patients with mild renal insufficiency [132]. The majority of these patients received benzbromarone. It is unclear whether this effect can be attributed to reduced serum uric acid levels since benzbromarone itself may directly suppress cyst growth by inhibiting the Ca^{2+} activated $Cl-$ channel TMEM16A, resulting in decreased transepithelial chloride secretion [142]. In contrast, a Korean cohort study that included 364 ADPKD patients reported that the use of febuxostat, but not allopurinol or benzbromarone, was associated with higher baseline eGFR [143]. The results of this study are difficult to interpret due to its cross-sectional nature. In addition to these retrospective studies, a phase 2/3 trial was recently announced to evaluate the effect of oxypurinol in ADPKD patients [144].

5.8 Other Agents

Several other agents are being investigated in clinical trials for use in ADPKD. In addition to their cholesterol-lowering effects, statins have other properties that could benefit patients with chronic renal disease, such as anti-oxidative and anti-inflammatory effects [145, 146]. Recently, a systematic review examined the effect of statin therapy on ADPKD progression and did not find a significant effect on annual TKV growth or eGFR decline, although urinary protein excretion and serum low-density lipoprotein levels were reduced [147]. A phase 4 placebo-controlled RCT is currently recruiting to examine the effect of pravastatin on TKV148. In addition, a phase 2 open-label study is evaluating the effect of pravastatin in combination with sodium citrate in 30 ADPKD patients with evidence of metabolic acidosis [149]. Primary endpoints of this study are changes in kidney function, liver function, and safety.

Pioglitazone is a thiazolidinedione and acts as a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist. This nuclear receptor forms a heterodimer with retinoic acid receptor A to control the transcription of multiple target genes. In addition to its insulin-sensitizing effects, pioglitazone may inhibit cystogenesis in animal models through several mechanisms, including the inhibition of CFTR expression and downregulation of proliferative pathways [150]. The PIOPKD study was a phase 1b placebo-controlled crossover study that evaluated the safety of low-dose pioglitazone treatment in 18 non-diabetic ADPKD patients [151]. In this pilot study, pioglitazone at a dose of 15 mg/day for 1 year appeared safe. Treatment with pioglitazone was followed by 1-year double-blind placebo treatment (or vice versa). No effects of pioglitazone on TKV or renal function were seen compared to placebo treatment, although the study was not sufficiently powered to detect such effects.

Tesevatinib (KD019) belongs to the class of tyrosine kinase inhibitors and is currently being investigated in a placebo-controlled phase 2 clinical trial [152]. It is a multikinase inhibitor that decreases the phosphorylation of c-Src, EGFR, and Erb2, and thereby reduces cellular proliferation in polycystic mice [153]. By targeting multiple pathways that are important to the pathophysiology of ADPKD, tesevatinib

may be an effective therapeutic strategy. However, phase 1 data presented at the American Society of Nephrology 2015 annual meeting reported frequent adverse events such as QT-prolongation, and side effects that are typically associated with EGFR inhibition like diarrhea and an acneiform rash [154]. The primary endpoint of this phase 2 trial are changes in htTKV. The study was completed in January 2022, and its results have not yet been published.

Bosutinib (SKI-606) is a dual Src/Bcr-Abl tyrosine kinase inhibitor and was approved for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia. Preclinical data indicated that inhibition of c-Src with bosutinib ameliorates renal cyst formation in two animal models [155]. A randomized, placebo-controlled clinical trial in 172 ADPKD patients showed a reduction of kidney growth in patients treated with bosutinib at 200 mg/day versus placebo, but unfortunately no significant effect on annual eGFR decline was found [156]. Adverse events were frequently encountered and led to a protocol amendment that reduced the bosutinib dose in 24 patients who were initially randomized to receive 400 mg/day. Treatment-related adverse events were responsible for 94% of study discontinuations in bosutinib 400 mg/day (n = 17 of 18) versus 60% in bosutinib 200 mg/day (n = 9 of 15), compared to 43% for placebo (n = 3 of 7). The most frequent adverse events were diarrhea and hepatocellular toxicity. Since then, new studies to investigate the effect of bosutinib in ADPKD have not been announced.

Curcumin is a naturally occurring polyphenol with antioxidative, anti-inflammatory, and anti-proliferative properties that have been extensively studied in multiple diseases [157]. These effects are exerted by its influence on various cellular signaling pathways, some of which are also dysregulated in ADPKD, including mTOR, NF-κB, MAPK, and Wnt signaling [158–160]. In tamoxifen-inducible *PKD1*-knockout mice, treatment with curcumin reduced cystogenesis and delayed renal failure [161]. Two additional animal studies have demonstrated beneficial effects of curcumin on ADPKD disease progression [162, 163]. Recently, a randomized, placebo-controlled clinical trial in 68 children and young adults with ADPKD was performed to examine the effect of daily oral curcumin supplementation (25 mg/kg per day) for 12 months on surrogate markers of vascular endothelial dysfunction and arterial stiffness [164]. This study failed to show any benefit on flow-mediated dilation of the brachial artery (p = 0.48), nor on pulse-wave velocity (p = 0.67) or total kidney volume. Despite the use of a formulation with enhanced bioavailability, the discrepant results between experimental studies and this clinical study may be explained by the fact that curcumin has very low oral bioavailability with extensive first-pass metabolism [165]. In experimental studies, high oral doses of curcumin were utilized (curcumin was

given in a dose equal to 1% of food intake in a previous experimental study [161]), but it is questionable whether such high oral dosing or parenteral administration are feasible and tolerable in humans.

6 Extrapolating Treatment Efficacy from Animal Models

Animal models of ADPKD offer valuable insights into the pathogenesis of ADPKD and are an essential part of the development of new treatment options for humans. Multiple rodent ADPKD models have been developed for preclinical testing, including models without *PKD1/PKD2* mutations, models with reduced *PKD1/PKD2* expression or missense mutations, and models with germline or conditional *PKD1/PKD2* gene knockouts. While these models seek to recreate human ADPKD, which itself is already a clinically and genetically heterogeneous disease, differences in key aspects such as lifespan, metabolism, renal anatomy, involved nephron segments, and genetics mean that rodent PKD models only partially resemble human ADPKD [166]. As such, novel therapies like mTOR inhibitors, somatostatin analogues, or curcumin may produce promising results in rodent models but subsequently fail to demonstrate meaningful effects in human ADPKD [22, 28–31].

Conversely, a single preclinical study with a novel medicament that suggests harmful effects in experimental ADPKD can potentially lead to the unjustified exclusion of ADPKD patients from large clinical trials. Examples are the DAPA-CKD and EMPA-KIDNEY studies [167, 168]. The DAPA-CKD found a promising attenuated rate of kidney function decline with the SGLT2 inhibitor dapagliflozin in subjects with chronic kidney disease and an elevated ACR. Unfortunately, these trials excluded subjects with polycystic kidney disease, because an experimental study suggested that dapagliflozin may aggravate polycystic kidney disease in PCK rats [169]. This precludes a post hoc analysis of the effect of SGTL2 inhibitors in ADPKD.

Given the many and sometimes fundamental differences between human ADPKD and animal disease models, the exclusion of ADPKD patients from large clinical trials in chronic kidney disease based solely on a single animal study is, in our opinion, unjustified. To do so, harmful effects would have to be demonstrated in several different experimental models. In addition, when taking into account the essential differences between the available rodent models, the results of a single negative study are also not sufficient to stop developing a drug, nor should the results of a single positive study suffice to move drug development from the preclinical to the clinical phase. The question then arises which and how many rodent PKD models should be tested before proceeding to human trials. Although this

question has no definitive answer, the use of at least two different models, preferably a model with germline hypomorphic or missense mutations in combination with an inducible conditional knockout model, has been suggested [166].

7 Conclusion

As we have described above, several drugs have been or are being developed as renoprotective treatment in ADPKD. Since ADPKD is a complex disease with a high degree of genetic heterogeneity, and the mechanisms implicated in cyst growth also have important functions in various physiological processes throughout the body, it may be difficult to design new interventions that effectively target cyst growth and preserve kidney function without causing major adverse events. Since lifelong treatment is required in ADPKD, only a minimal degree of adverse events is acceptable. Options to overcome these difficulties are additional interventions to decrease adverse events, for instance in case of vasopressin 2 receptor antagonists, or to design drugs that can be selectively transported into renal cysts. Advancements in the knowledge of the pathophysiology of the disease, as well as better insight in the process of drug development, will hopefully bring new treatments to prevent the need for kidney replacement therapy in ADPKD patients.

Declarations

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