

The impact of tolvaptan on autosomal dominant polycystic kidney disease – literature review

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Abstract

This article presents current data from international literature on the impact of tolvaptan on autosomal dominant polycystic kidney disease (ADPKD). The authors have reviewed the latest clinical research literature. Additionally, the paper discusses the molecular biology of ADPKD and the effects of tolvaptan use on liver and kidney function, and presents the treatment of the described disease in adults and children. Complications of tolvaptan treatment are also briefly discussed.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a genetically determined disease inherited in an autosomal dominant manner. The disease results from mutations in the PKD1, PKD2, and less frequently, GANAB and DNAJB11 genes [1]. Mutations in PKD1 and PKD2 cause the loss of polycystin-1 and polycystin-2, which leads to a decrease in intracellular calcium concentration. This increases the activity of adenylate cyclase types 5 and 6, reduces the activity of phosphodiesterase 1, and increases the level of cyclic adenosine-3', 5'-monophosphate (cAMP), leading to the formation of cysts in the kidneys [2]. ADPKD is characterised by the presence of numerous cysts within the cortex and medulla of both kidneys [2]. It has been found that cysts can form even in the foetus, resulting in the development of early symptoms of ADPKD in newborn children [3, 4]. This condition is the fourth most common disease in adults leading to end-stage renal failure. The incidence of ADPKD is estimated at 1 : 400 to 1 : 1000 [5]. It is usually diagnosed in individuals between the ages of 10 and 30 years [6]. The most common symptoms of ADPKD include hypertension (HTN), flank pain, and haematuria.

The occurrence of rare mutations, including in the GANAB and DNAJB11 genes, is associated with concomitant polycystic liver disease (ADPLD), and in the case of the latter, also with features characteristic of autosomal dominant tubulointerstitial diseases (ADTKD), such as the absence of renal enlargement and histologically visible interstitial fibrosis in

the noncystic parenchyma [7, 8]. Normal kidney size in the case of DNAJB mutations means that the disease is diagnosed much later than in the case of mutations in the PKD1 and PKD2 genes [8]. Progression of ADPKD to end-stage renal failure typically occurs after the age of 60 years in untreated patients [9].

Molecular biology of ADPKD

ADPKD is most often the result of mutations in the PKD1 and PKD2 genes, causing the loss of polycystin-1 and polycystin-2. This leads to a decrease in intracellular calcium and cAMP levels and thus to the formation of kidney cysts. Tolvaptan provides therapeutic benefits mainly by inhibiting intracellular cAMP production in the kidney [10]. Importantly, studies in mice indicate that the presence of additional triggering factors, such as acute kidney injury (AKI), is necessary to initiate the formation of kidney cysts, and oxidative stress is responsible for the progression of the disease [11, 12].

Studies published in 2022 indicate that the highest level of oxidative stress occurs in untreated patients with ADPKD, compared to those treated with tolvaptan and healthy individuals. Protein expression of p22phox in mononuclear cells, phosphorylation of MYPT-1, and the amount of HO-1 protein were examined. The expression of p22phox protein was highest in untreated ADPKD patients at 1.42 ± 0.11 ($p = 0.015$), in patients treated with tolvaptan it was 0.86 ± 0.15 ($p = 0.015$), and in healthy individuals it was 0.53 ± 0.11 ($p < 0.001$). Beneficial effects of tolvap-

tan were also noted in other marker studies. This study indicates that treatment of ADPKD patients with tolvaptan lowers the level of oxidative stress and contributes to slower loss of kidney function.

Treatment

Before the approval of tolvaptan, the treatment of patients with ADPKD was limited to controlling blood pressure, lifestyle changes, and treating symptoms such as pain and complications of the disease. A few years ago, the US Food and Drug Administration (FDA) approved tolvaptan for the treatment of adults with rapidly progressing ADPKD [12]. Tolvaptan is a vasopressin V2 receptor antagonist. Its mechanism of action involves inhibiting the formation of cyclic adenosine-3', 5'-monophosphate (cAMP), which limits the growth of kidney cysts [13]. A meta-analysis of thirteen studies conducted in 2023 compared the effectiveness of tolvaptan versus placebo in treating patients with ADPKD. The doses of tolvaptan varied, ranging from 30 mg to 90 mg in the morning and from 15 mg to 30 mg in the afternoon. Tolvaptan was shown to be effective in terms of slowing the decline in eGFR (MD = 1.27, 95% CI: 1.24–1.29, $p < 0.01$), reducing the increase in TKV (total kidney volume) (MD = -3.01, 95% CI: -3.55 to -2.47, $p < 0.01$), and reducing some complications. These include urinary tract infection (OR = 0.69, 95% CI: 0.54–0.89, $p < 0.01$), hypertension (OR = 0.66, 95% CI: 0.52–0.82, $p < 0.01$), flank pain (OR = 0.71, 95% CI: 0.58–0.87, $p < 0.01$), and haematuria (OR = 0.68, 95% CI: 0.51–0.89, $p < 0.01$). It was observed that patients treated with tolvaptan more frequently experienced complications such as increased thirst (OR = 8.48, 95% CI: 4.53–15.87, $p < 0.01$), polyuria (OR = 4.71, 95% CI: 2.17–10.24, $p < 0.01$), and liver damage (OR = 4.56, 95% CI: 2.51–8.29, $p < 0.01$) [14].

In a TEMPO trial, 17% of CKD type 1, 14.6% of CKD type 2, and 14.7% of CKD type 3 patients treated with tolvaptan discontinued study treatment due to adverse events, compared with 5.8%, 4.9%, and 3.5% of placebo-treated patients [15]. It is therefore possible that adverse events resulting from aquaresis may contribute to nonadherence to tolvaptan therapy. However, adverse effects such as polydipsia and polyuria did not significantly worsen patients' quality of life [16].

In the NOCTURNE study, mean ADPKD-UIS scores indicated no deterioration in quality of life, and ADPKD-IS and SF-12v2 scores showed minimal changes during the treatment period [17]. A low salt and protein diet and adjustments to the timing of doses are strategies to manage the urinary burden of tolvaptan therapy [16, 18]. Adverse events associated with aquaresis become more tolerable with continued treatment [19].

Liver damage mainly occurred between the 60th and 240th day of treatment with tolvaptan. For this reason, frequent monitoring of liver parameters is rec-

ommended, and if liver function deteriorates, treatment should be discontinued [20]. Tolvaptan has been shown to be effective in patients at both early and late stages of ADPKD progression. The meta-analysis showed a slowing of TKV growth in patients with ADPKD and CKD in stages one, two, and three. It is believed that increased thirst and polyuria, considered adverse effects of tolvaptan treatment, reduce the frequency of urinary tract infections, kidney stones, haematuria, and flank pain. Thus, they have beneficial effects in patients with ADPKD [20].

According to other studies, tolvaptan as a vasopressin V2 receptor antagonist does not increase the production of renin and aldosterone, which results in a reduced frequency of hypertension in patients with ADPKD [21]. Contraindications for the use of tolvaptan include uncontrolled hypernatraemia, liver function disorders, pregnancy, lactation, inability to perceive thirst, hypovolaemia, urinary tract obstruction, and concurrent use of strong CYP3A inhibitors such as ketoconazole, clarithromycin, and ritonavir. When using moderate CYP3A inhibitors such as amiodarone, erythromycin, verapamil, or imatinib, a reduction in the dose of tolvaptan is necessary. Breastfeeding is not recommended for women taking tolvaptan [12].

Non-pharmacological treatment may also play an important role in the treatment of ADPKD. In addition to impaired cAMP production and increased oxidative stress, cells in ADPKD also exhibit abnormal, increased glucose metabolism via aerobic glycolysis (Warburg effect) [22]. This fact may prove to be the key to another therapeutic strategy. Introducing ketosis through daily calorie restriction (DCR), intermittent fasting (IMF), time-restricted feeding (TRF), and a ketogenic diet (KD) is potentially effective in patients with ADPKD to slow down disease progression thanks to an alternative energy source to glucose, which is fat [21]. Dietary salt restriction may also have a significant impact on the course of the disease. Protein restriction is still a controversial issue [23]. Increased water intake reduces plasma arginine vasopressin (AVP) levels, which is likely to be beneficial for preserving renal function, but this recommendation seems controversial [24]. It is also recommended that caffeine be avoided in all ADPKD patients because caffeine-induced inhibition of phosphodiesterase increases cAMP accumulation.

New therapeutic strategies

Currently, gene therapies are being studied, the therapeutic targets of which are miRNAs, inhibition of DNA methylation, and gene therapy. MicroRNAs (miRNAs) are non-coding RNAs (ncRNAs) that function as inhibitors of post-transcriptional mRNA expression [25]. Animal studies have shown that abnormal expression of miR-17 and miR-21 in mice causes PKD by directly inhibiting the expression of PKD1 and PKD2, and anti-

miR-17 and anti-miR-21 therapy slows down cyst growth in mice with PKD1 and PKD2 mutations [26, 27].

In ADPKD, hypermethylation of the PKD1 gene promoter and within the gene-body regions of PKD1 and other genes related to iron transport and cellular adhesion has been demonstrated [28–30]. These changes are responsible for the decreased expression of PKD1 and the development of renal cysts. In the study by Woo *et al.*, increased expression of PKD1 was achieved by inhibiting DNA methylation using 5-aza-2'-deoxycytidine, which contributed to the reduction of cyst development [30].

Kurbegovic *et al.* developed a one-copy hybrid transfer, with a renal-specific SB minimal regulatory region substituting for the Pkd1 upstream region, which significantly delays the appearance of cysts, slows its progression, delays renal failure, and prolongs life by 4 to 25 times or completely overcomes the genetic deficiency of PKD [31].

Monitoring treatment efficacy and disease progression

The progression of the disease and the efficacy of tolvaptan treatment can be assessed using eGFR [35]. Another parameter for assessing disease progression is the increase in total kidney volume (TKV). In ADPKD, TKV can increase even before a decrease in eGFR occurs. Annual measurements of TKV are not recommended in the literature because they may lead to varied results. Currently, it is suggested that a CT or MRI be performed every 3–5 years to monitor TKV growth [32].

A study published in 2018 evaluated whether the level of endogenous somatostatin concentration impacts the progression of ADPKD [33]. Changes in plasma somatostatin levels during treatment with lanreotide (a synthetic somatostatin analogue) and tolvaptan were also examined. It was found that plasma somatostatin levels are not associated with disease progression, but they decrease during treatment with lanreotide. In patients treated with tolvaptan, somatostatin levels do not change. Further research is needed to confirm whether somatostatin concentration measurements can be used as a marker in monitoring the efficacy of therapy in patients treated with lanreotide.

In an article published in 2023, the use of Dickkopf 3 (DKK3) glycoprotein in monitoring the progression of disease in patients with ADPKD was described [34]. The use of this glycoprotein as a biomarker to estimate the risk of kidney function loss has been described in several studies, but these did not consider patients with ADPKD. DKK3, influenced by oxidative stress through the Wnt pathway, leads to tubulointerstitial fibrosis. This study showed significantly higher levels of DKK3 in patients with ADPKD compared to a control group. The level of DKK3 also correspond-

ed to the degree of disease in the Mayo classification (which allows for the assessment of the risk of disease progression based on the patient's age and total kidney volume adjusted for patient height). The level of DKK3 was significantly higher in patients with ADPKD treated with tolvaptan than in the untreated group. This difference may result from the classification of patients for the study and the criteria for admission to tolvaptan treatment, as patients taking tolvaptan have a higher Mayo classification score and more advanced chronic kidney failure. Further research involving a larger number of patients with ADPKD is recommended to confirm these results. This could enable the future use of biomarkers to monitor and predict the course of the disease, instead of performing more time-consuming imaging studies.

Impact of tolvaptan on liver function

It has been shown that the highest risk of liver function disturbances in patients with ADPKD occurs during the first 18 months of treatment [35]. If such abnormalities are observed, the dose of the medication should be reduced or discontinued.

Based on the TEMPO 4:4 study, in which some patients treated with tolvaptan experienced liver function disturbances, the Independent Data Monitoring Committee recommended increasing the frequency of liver parameter monitoring to monthly for patients treated with tolvaptan for less than 18 months, and then every 3 months thereafter [36].

Tolvaptan was approved in European Union countries based on the TEMPO 3:4 study, whereas the FDA did not approve tolvaptan for the treatment of ADPKD patients based on this study. In 2018, the FDA approved the use of tolvaptan in patients with rapidly progressing ADPKD, recommending monitoring of ALT, AST, and bilirubin every 2 weeks for the first month of treatment, then monthly for 18 months, and quarterly thereafter [32].

The REPRIS (Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy) study was conducted, among other reasons, to monitor whether adverse effects occur in patients with ADPKD treated with tolvaptan, to check if the drug can be safely used, and whether it is effective. Liver parameters were checked monthly. Elevated values were observed in 5.6% of patients. However, these did not meet Hy's law criteria (for the criteria to be met, ALT should be 3 times above normal, serum bilirubin 2 times above normal, and jaundice must be present) [20].

In another study conducted by Torres *et al.*, a REMS (Risk Evaluation and Mitigation Strategy) protocol was used to quickly detect signs of liver damage in patients using tolvaptan. The study involved 1800 patients, with the median duration of tolvaptan use being 651 days. ALT, AST, and GGTP were tested

according to the accepted schedule (monthly up to the 18th month of treatment, then quarterly). Elevated ALT values were found in 2.8% of patients, GGTP in 1.1%, and AST in 0.6% of patients. Patients with abnormalities did not meet Hy's law criteria. Treatment with tolvaptan was discontinued in 0.6% of patients with these deviations. It was demonstrated that taking statins did not increase the risk of liver function disturbances. During the study, a Hepatic Adjudication Committee (HAC) was appointed to determine the relationship between liver function disturbances and tolvaptan intake [37].

A procedure was described for cases of liver damage due to tolvaptan treatment, which assumes liver function improvement 4 months after discontinuation of the drug [35]. Severe liver injury with tolvaptan is rare. However, to prevent its occurrence, frequent monitoring of liver function tests is essential, especially during the first 18 months. If laboratory abnormalities or clinical symptoms suggestive of liver toxicity occur, the drug should be discontinued [38]. Because monitoring of liver markers is not useful in predicting idiosyncratic DILI, studies to detect specific biomarkers of DILI, conducted by the US Predictive Safety Testing Consortium (PSTC) managed by the Critical Path Institute and the European Safer and Faster Evidence-based Translation (SAFE-T) Consortium sponsored by the Innovative Medicines Initiative, seem promising [39].

Impact of tolvaptan on kidney function

The study by Torres *et al.* (TEMPO 3:4), published in 2016, demonstrated the long-term effects of tolvaptan: a slowdown in the rate of total kidney volume (TKV) growth was observed over 3 years [15]. The study involved patients with CKD with an eGFR above 60 ml/min/1.73 m². It was shown that the annual kidney volume increase in patients treated with tolvaptan was 2.8%, compared to 5.5% in patients taking a placebo ($p < 0.001$). The degree of kidney function deterioration was also compared by measuring the reciprocal of serum creatinine concentration. The annual worsening of kidney function was -2.61 mg/ml with treatment and -3.81 mg/ml without treatment with tolvaptan [40, 41].

Long-term observations by Edwards and Torres (TEMPO 4:4) showed that tolvaptan demonstrates sustained efficacy in treating patients with ADPKD by delaying the decline in eGFR [36, 42].

In 2021, Torres *et al.* published a retrospective study comparing the decline in eGFR among patients treated with tolvaptan and those receiving placebo. The baseline eGFR in both groups ranged from 15 to 29 ml/min/1.73 m². The average annual decline in eGFR in patients treated with tolvaptan was -3.4, and it was -5.2 in those receiving placebo ($p < 0.001$). The decline in eGFR was also compared among patients with an ini-

tial eGFR above 30 ml/min and continued treatment after a decline in eGFR to levels between 15 to 29 ml/min/1.73 m². However, no differences were observed in the average annual declines in eGFR among these patients [43]. Based on the described study, it was concluded that treating patients with ADPKD (with an eGFR level from 15 to 29 ml/min/1.73 m²) with tolvaptan significantly delays the decline in eGFR.

The REPRIS study was conducted over a 12-month period in patients with more advanced stages of CKD (eGFR 25 to 65 ml/min/1.73 m²). The study demonstrated that tolvaptan is beneficial for patients at such levels of eGFR and proved that it can be used in patients with eGFR down to 25 ml/min/1.73 m² [20].

Twenty-five percent of patients with ADPKD develop kidney stones. The stones typically consist of calcium oxalate or uric acid. Patients with kidney stones are at risk of developing a greater number of larger cysts, leading to an increase in kidney volume [44, 45]. Tolvaptan's mechanism of action causes polyuria, which to some extent protects against the development of kidney stones [46]. A study by Cheungpasitporn *et al.* showed that tolvaptan reduces the saturation ratio for calcium oxalate, calcium phosphate, and uric acid in kidney stones [47].

Bargagli *et al.* conducted a study that demonstrated the association of tolvaptan use with polyuria, elevated plasma copeptin levels, reduced relative saturation indices for calcium phosphate, calcium oxalate, and uric acid, and increased urinary citrate excretion. Tolvaptan also increased urinary calcium excretion [48, 49].

Use of tolvaptan in children with ADPKD

Developing an optimal treatment for ADPKD in the paediatric population is extremely important, especially in the youngest group of patients. It has been shown that children with very early onset ADPKD (VEO-ADPKD) are more likely to have hypertension, lower estimated glomerular filtration rate (eGFR), and larger age-corrected kidney volume in ultrasound examination compared to older children [50]. Early treatment has a very significant impact on the course of the disease by minimising long-term complications [51, 52].

A yearly, randomised, double-blind study published in January 2023 assessed the safety and efficacy of tolvaptan in children with ADPKD [53]. The study primarily focused on individuals from 12 to 17 years of age with ADPKD, with an eGFR above 60 ml/min/1.73 m², with a number of kidney cysts equal to or greater than 10 and dimensions above 0.5 cm in magnetic resonance imaging (MRI). Patients were administered placebo or various doses of tolvaptan depending on body weight and treatment tolerance. Tolvaptan was taken twice daily in 2 different doses. Initially, small doses were used, which were gradually increased. The initial and maximum doses were, respectively,

30/15 mg and 45/15 mg for individuals weighing above 45 kg but below 75 kg. Patients weighing above 75 kg received an initial dose of 45/15 mg, then a maximum of 60/30 mg. At any point in the study, a patient could reduce the treatment dose if they had a problem with its tolerance. The parameter assessed was the change in total kidney volume adjusted for the child's height. In the group of patients treated with tolvaptan, this index was 2.6%, and in the placebo group, it was 5.8% ($p > 0.05$). Changes in eGFR were also measured. It was 1.9 ml/min/1.73 m² in patients treated with tolvaptan and -1.8 ml/min/1.73 m² in those receiving placebo. In the tolvaptan group, complications related to polyuria and polydipsia occurred more frequently (65%) than in children receiving placebo (16%). Hypernatraemia occurred in 2% of patients treated with tolvaptan. No liver function disturbances or deterioration in the quality of life in children were observed. Seven participants withdrew during the study (4 from the tolvaptan group and 3 from the placebo group). It was concluded that tolvaptan is effective and safe in treating children with ADPKD.

In 2017, a case of a newborn with a severe form of ADPKD, with significant enlargement of the kidneys and breathing disorders was reported. The child also had hyponatraemia. Treatment with tolvaptan improved the overall condition of the child. Hyponatraemia resolved, and no further enlargement of the kidneys was observed in ultrasound examinations. It was concluded that tolvaptan could be used in the treatment of newborns with ADPKD [54].

However, to date, few studies have been conducted on the treatment of children and adolescents with tolvaptan.

Complications of tolvaptan treatment

Common complications of treating patients with ADPKD with tolvaptan include urinary tract infections, hypertension (HTN), flank pain, haematuria, increased thirst, polyuria, and liver damage [15]. In the TEMPO 3:4 study, additional less common side effects included skin malignancy, glaucoma, pharyngitis, urinary tract obstruction, upper respiratory infections, and excessive fatigue. Some of these complications did not occur in a long-term observational study conducted later, published in 2021 [37].

Another medication among those included in the clinical trial (NCT04152837) is lixivaptan, which is also a V2 receptor antagonist. This group of patients includes those who experienced abnormal liver parameter values during treatment with tolvaptan. Toxicology modelling studies suggest a favourable safety profile. Further studies are needed to assess its usefulness in the treatment of ADPKD [54, 55].

A 2022 article highlighted the beneficial effects of the somatostatin analogue octreotide in the treatment of patients with ADPKD. This drug has only been

approved for use in Italy [56]. A 2020 article described the use of somatostatin analogues (octreotide, lanreotide, pasireotide) in treating patients with ADPKD [57]. Somatostatin inhibits the production of intracellular cAMP and the release of aldosterone and renin. Due to these actions, preclinical and preliminary clinical studies have shown the potential use of somatostatin analogues in patients with ADPKD. However, another study did not demonstrate any beneficial effect of lanreotide in treating patients with late-stage ADPKD. Treatment with somatostatin analogues is associated with numerous side effects, mainly gastrointestinal and circulatory. The ALADIN study suggests that prolonged-release octreotide may delay the progression of renal failure and may be an alternative to tolvaptan therapy, especially since its use was associated with less severe adverse events, such as diarrhoea and gallstone formation [58]. It has been shown that these symptoms decrease with the duration of therapy. The use of somatostatin analogues in treating patients with ADPKD requires further research. The TAME-PKD study focuses on the potential usefulness of metformin in the treatment of ADPKD and the incidence of adverse events, especially gastrointestinal events [59].

In 2023, the influence of plant-derived compounds in treating patients with ADPKD was also described [60]. Compounds that may delay the development of kidney cysts include saikosaponin-d, curcumin, ginkgolide B, resveratrol, Ganoderma triterpenes, Cordyceps sinensis, triptolide, quercitrin, steviol, naringin, cardamonin, Sparganium stoloniferum Buch.-Ham, olive leaf extract, and gambogic acid. It has been found that metformin, derived from Galega officinalis, may delay the progression of ADPKD. The use of plant-derived compounds requires detailed clinical studies to assess the efficacy and safety of these drugs *in vivo*.

Summary

Numerous studies have proven that tolvaptan prolongs the period during which there is a decline in eGFR and an increase in TKV. The most serious complication of treatment with this drug is liver function disorders, leading to liver failure. Tolvaptan reduces the occurrence of spinal flank pain, urinary tract obstruction, and HTN in patients, but it causes polyuria and polydipsia. Further research is still necessary to better understand the action of tolvaptan.

Conclusions

Further research is necessary on the use of tolvaptan in treating children and adults with ADPKD. The use of tolvaptan in treating patients with ADPKD influences the slowing down of the decline in eGFR and delays the increase in TKV. The most common adverse effects of tolvaptan treatment do not significantly lower the quality of life for patients.

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Conflict of interest

The authors declare no conflict of interest.

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