

Tolvaptan in Pediatric Autosomal Dominant Polycystic Kidney Disease: From Here to Where?

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Keywords

Tolvaptan · Autosomal dominant polycystic kidney disease · Children · Therapy

Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder, accounting for approximately 5% of all ESRD cases worldwide. As a vasopressin receptor 2 antagonist, tolvaptan is the FDA-approved therapeutic agent for ADPKD, which is only made available to a limited number of adult patients; however, its efficacy in pediatric patients has not been reported widely. **Summary:** Tolvaptan was shown to delay ADPKD progression in the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 study, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial, and other clinical studies. In addition to its effects on aquaretic adverse events and alanine aminotransferase elevation, the effect of tolvaptan on ADPKD is clear, sustained, and cumulative. While ADPKD is a progressive disease, the early intervention has been shown to be important and beneficial in hypotheses as well as in trials. The use of tolvaptan in pediatric AD-

PKD involves the following challenges: patient assessment, quality of life assessment, cost-effectiveness, safety, and tolerability. The ongoing, phase 3b, 2-part study (ClinicalTrials.gov identifier: NCT02964273) on the evaluation of tolvaptan in pediatric ADPKD (patients aged 12–17 years) may help obtain some insights. **Key Messages:** This review focuses on the rationality of tolvaptan use in pediatric patients with ADPKD, the associated challenges, and the suggested therapeutic approaches.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a monogenetic progressive kidney disease with an incidence ratio of nearly 1:400–1,000, and it is the fourth most common cause for renal replacement therapy worldwide [1–4]. To date, ADPKD is known to be caused by the mutations in the *PKD1*, *PKD2*, *GANAB*, and *DNAJB11* genes [5–7]. It is characterized by the progressive, bilateral development and enlargement of renal cysts and increased kidney volume, which eventually leads to ESRD. The progressive loss of kidney function takes place over several decades, about 50% of patients

developing ESRD by 65 years of age, and approximately 3% of children have either very early onset or an unusually rapidly progressing form of the disease owing to the unusual genetic constellations [8, 9]. Children with very early onset-ADPKD represent a particularly high-risk group among patients with ADPKD [10].

The disease course commences in childhood with the symptoms of hypertension, proteinuria, and urinary concentration defects and may be accompanied by early-onset renal failure in some cases. The kidney volume increases by an average of 5.27% per year, which could indicate disease progression before a measurable decline in function [11]. Given the fact that parenchymal destruction occurs in the form of compensated glomerular filtration rate (GFR) values, the most reasonable method for the long-term preservation of renal function is to initiate treatment as early as possible. Based on these findings, early interventions are beneficial and necessary, and early treatment may have the potential to delay renal dysfunction progression.

Treatments to slow disease progression in children with ADPKD are limited, and some studies conducted on children with ADPKD have shown an elevated incidence of hypertension, proteinuria, and left ventricular hypertrophy, as the risk factors to disease progression, which are amenable to treatment [12, 13]. Preclinical studies have shown the role of arginine vasopressin-mediated cAMP production as a driver of cyst proliferation and fluid secretion in ADPKD. Tolvaptan is a highly selective V2 receptor antagonist that regulates cAMP levels to inhibit both epithelial cell proliferation and Cl⁻ excretion, which induces cyst expansion. Higher rates of kidney enlargement are associated with a more rapid decline in renal function [14], and the total kidney volume (TKV) is a valuable biomarker for gauging treatment effects in clinical trials and is more sensitive to disease progression than GFR or serum creatinine [15].

Milestones in ADPKD Treatment with Tolvaptan

Tolvaptan has been studied in animal models of PKD and has been shown to delay the progression of PKD [16, 17]. The results of the TEMPO 3:4 study and the REPRISÉ trials show that tolvaptan delays the increase in TKV and the decline in kidney function in patients with ADPKD [18, 19]. In the phase III TEMPO 3:4 trial (entry criteria: ADPKD aged 18–50 years, with TKV \geq 750 mL and estimated creatinine clearance \geq 60 mL/min), tolvaptan treatment for 3 years delayed the increase in TKV and the de-

cline in renal function relative to that achieved by placebo; in the TEMPO 4:4 extension trial, the effect of tolvaptan in delaying the decline in renal function was maintained for a further 2 years. The phase III REPRISÉ trial confirmed the efficacy of tolvaptan in patients with late-stage ADPKD (entry criteria: ADPKD aged 18–55 years with a baseline eGFR of 25–65 mL/min/1.73 m² and ADPKD aged 56–65 years with an eGFR of 25–44 mL/min/1.73 m² and eGFR decline of $>$ 2.0 mL/min/1.73 m² per year). The effect of tolvaptan on eGFR is sustained, cumulative, and consistent with potential delays in the need for kidney replacement. Tolvaptan is currently approved for the treatment of rapidly progressive disease in adult patients with ADPKD in Japan, Canada, the European Union, the USA, and Korea [20].

Rationale for Early Treatment

ADPKD is not usually clinically diagnosable until it ultimately leads to ESRD. Evidence from the pathogenesis of cyst formation shows that early fetal cyst formation is an important feature of ADPKD [21], and it expands continuously over a lifetime. While the loss of glomeruli may begin in utero or in childhood, in most patients, it proceeds at a relatively slow rate that does not lead to renal failure for 5 or 6 decades. Early-stage cysts may indicate past renal injuries [22, 23]; meanwhile, individuals with ADPKD exhibit normal or mildly decreased GFR (KDOQI stages 1–2) for several decades. Children with ADPKD demonstrate a higher rate of increase in TKV than adults [24], and the kidney volume is confirmed to be a marker of ADPKD progression. Models of changes in TKV suggest that treatment initiation with tolvaptan at earlier stages of the disease (eGFR $>$ 60 mL/min/1.73 m²) could exert a more significant effect on kidney function preservation than treatment starting at later stages [25]. The beneficial effects of early treatment on slowing cyst formation have been demonstrated in preclinical models and in patients requiring blood pressure control [26, 27]. Early intervention may not only be the best choice for improving renal outcomes, but may also potentially delay renal dysfunction progression.

Trials and Case Studies on Pediatric ADPKD

A post hoc analysis in the TEMPO 3:4 trials revealed that tolvaptan can serve as a safe and effective treatment agent in patients with ADPKD aged 18–24 years [28]. An

Table 1. Suggestions for tolvaptan administration in different guidelines

Study	Country	Year	Suggestion for tolvaptan
Gimpel et al. [35]	Multiple	2019	High risk of early progression
Dudley et al. [36]	UK	2019	None
Chebib et al. [37]	USA	2019	No specifications on pediatric cases

There are no clear guidelines for the use of tolvaptan in pediatric ADPKD.

ongoing, phase 3b, 2-part study (ClinicalTrials.gov identifier: NCT02964273) is the first clinical study to evaluate the effects of tolvaptan in pediatric patients with ADPKD aged 12–17 years [29]. Although the study has some limitations (first, tolvaptan and placebo may lead the subject and/or investigator to perceive treatment assignment due to the difference in aquaretic effect, and it may need additional fluid intake to confound this effect, which could influence the endpoints. Second, the study inclusion criteria of ADPKD diagnosis and cyst burden are subjective. Finally, early tolvaptan discontinuation could happen in some patients, though the patients still have good renal function), it is expected to provide valuable information on the safety, tolerability, PD, PK, and efficacy of tolvaptan in pediatric patients with ADPKD. Cases of off-label use in pediatric ADPKD have been reported. A female infant with massive renal enlargement, respiratory compromise, and hyponatremia was treated with tolvaptan, which resolved hyponatremia, and there was no further increase in renal size noted [30]. This suggests the usefulness of tolvaptan for treating severe neonatal PKD. The second case of tolvaptan use is in a neonate with severe ADPKD in the UK; tolvaptan administration relieved edema, but the kidneys remained enlarged [31]. Tolvaptan has also been used to successfully treat pediatric syndrome of inappropriate antidiuretic hormone as well as severe hyponatremia in pediatric nephrotic syndrome [32–34].

Consensus for Pediatric Use

Several guidelines are available for ADPKD treatment in adults, whereas limited information is available on the treatment of children and adolescents with ADPKD (shown in Table 1). A network for early-onset cystic kidney disease (NEOCYST) suggests that vasopressin antagonists should not be administered routinely, but off-label use can be considered in selected pediatric patients. The off-label use of vasopressin antagonists can be considered at clinician discretion in children at a high risk of early

progression based on a high TKV, rapid kidney growth, and family history, among other symptoms [35]. The British guidelines for monitoring children and young people with or at a risk of developing ADPKD do not recommend medication [36]. In the USA, a practical guide for treatment of rapidly progressive ADPKD with tolvaptan provides practical guidance and discusses steps to consider before and after prescribing tolvaptan; however, it does not contain specifications on use in pediatric patients [37].

Remaining Problems

Although the benefits and side effects of tolvaptan have been discussed in multiple studies, it remains unclear if these results can be replicated in trials on pediatric patients. Most data on ADPKD are from studies conducted on adults, and confirmatory studies in pediatric patients are needed. In both the REPRISSE and TEMPO 3:4 trials, the most significant beneficial effects of tolvaptan on eGFR decline were observed in patients with a baseline eGFR >45 mL/min/1.73 m² (CKD stage 3a), the late stage, and the potential long-term benefits of the reduction in eGFR decline associated with tolvaptan therapy remain uncertain. There are remaining questions on the effects of tolvaptan on TKV and whether these effects might become negligible over several years of treatment [38], which is of more significance in children and adolescents.

The most common adverse event associated with tolvaptan use reported in previous studies was linked to hepatotoxicity; the levels of serum alanine aminotransferase or aspartate aminotransferase were found to be elevated in patients in the (TEMPO) 3:4, (TEMPO) 4:4, and (REPRISSE) trial. Though 3 patients had severe drug-induced liver injury, the long-term safety of tolvaptan was under control through regular monitoring [39]. Aquaretic adverse events (AEs) such as polyuria, thirst, nocturia, and polydipsia are also common [18, 40]. Treatment-emergent AEs (TEAEs) are time-related, and long-term

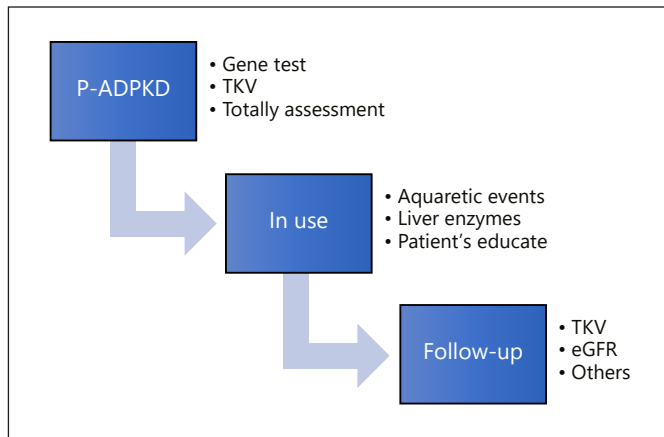


Fig. 1. The roadmap of tolvaptan use in pediatric ADPKD. P-ADPKD, pediatric autosomal dominant polycystic kidney disease; others: urine test, blood pressure monitoring, and clinical manifestations; TKV, total kidney volume.

exposure to tolvaptan had resulted in similar hepatic AEs and aquaretic TEAEs, as observed in previous studies [39]. However, the impact of this agent on liver enzymes in children is yet to be determined. Patients receiving tolvaptan were also reported to exhibit increased urinary shedding of heparin-binding EGF-like growth factor [41], as well as an increase in serum sodium and uric acid levels and gout frequency.

From the off-label use cases of tolvaptan in pediatric ADPKD, tolvaptan treatment was well tolerated and believed to be a safe treatment in all reported cases. Only polyuria was found in some cases, which is the expected outcome of tolvaptan use. Polyuria was found in a female infant treated for severe ADPKD, and there have been no incidents of hypernatremia or hepatotoxicity [30]. While tolvaptan produced the expected aquaresis and blood pressure reduction in another severe neonatal ADPKD case, no AEs were reported [31]. Kerling et al. [42] reported 1 case of hypernatremia which was reversible after 1 day in a study of tolvaptan for the treatment of neonates and infants with capillary leak syndrome after cardiac surgery.

Quality of life and cost-effectiveness are 2 primary concerns related to tolvaptan use, especially in pediatric patients. Aquaretic AEs such as polyuria, thirst, nocturia, and polydipsia could influence the patients' cooperation and adherence with access to water being more restricted. However, there are no details on quality of life from publications on tolvaptan. Only a limited number of studies have investigated the cost-effectiveness of tolvaptan usage in patients with ADPKD. A cost-effectiveness analy-

sis showed that tolvaptan could delay the onset of ESRD by 6.5 years and increase life expectancy by 2.6 years. However, given the current cost of the drug, it is not a cost-effective treatment strategy, as compared to the local gross domestic product value [43, 44]. Based on the dose of tolvaptan in an ongoing trial on pediatric patients with ADPKD [29], the average cost of tolvaptan is <30,000 EUR per year, whereas the gross domestic product per person in Germany is approximately 39,000 EUR currently.

Approach before Use

As tolvaptan is approved for use in adults at risk of rapidly progressing ADPKD, it is important to first identify cases of rapid progression. Currently, the number of strategies for the accurate and rapid identification of patients at a high risk of developing ESRD in adulthood is insufficient; further, there is no consensus on the management of children at a risk of developing ADPKD.

Clinical prognostic scoring based on age- and height-adjusted Mayo imaging classification (TKV) or on genotype, sex, and clinical symptoms (PROPKD score) has been established for adults only [45–47]. Based on these 2 models, the risk assessment of prognosis can be accomplished primarily using 2 separate approaches: TKV assessment and genetic testing. Given the fact that changes in TKV are not obvious in most pediatric patients, the acquisition of genetic information is more important.

As indicated in the “two hits” or the “cilla” theory, the genotype is related to the phenotype and the progression of ADPKD. Truncating PKD1 mutations, nontruncating PKD1 mutations, and PKD2 mutations are associated with the most severe, intermediate, and least severe forms of the disease, respectively [48, 49]. A study showed that patients with ADPKD and no PKD1/2 mutation showed minimal improvements in eGFR/year and in the annual rate of increase in TKV with tolvaptan [50]. Among children at a risk of ADPKD and no family history of the disease, 6–8% of cases of ADPKD have been found to be caused by de novo mutations [51, 52].

A better understanding of the gene mutation patterns not only has a prognostic value but also provides insights on risk factors for disease progression from an early disease stage [53]. However, the burden on the parents to care for a child diagnosed with the disease would lead to unnecessary anxiety and stress.

Conclusion

Although treatments to slow disease progression in children with ADPKD are limited, tolvaptan is a promising option, and children and young adults with ADPKD may represent a critical therapeutic window. The entry criteria, clinical prognostic scoring, and monitoring measurement have been established in adult ADPKD patients; nevertheless, the screening and monitoring methods in children are missing. Based on the experience in off-label uses in pediatric ADPKD, future tolvaptan use should focus on the individualized dosing and monitoring according to different age groups. Given the fact that there were no guidelines to follow, tolvaptan use in children could monitor hypertension, proteinuria, kidney volume, cyst volume (or number), and (estimated) GFR according to the international consensus statement on the diagnosis and management of ADPKD in children and young people [35]. Though severe side effects in tolvaptan use in pediatric ADPKD have not been reported, it needs large-sample study and long-term observation. The appropriate timing for treatment initiation is yet to be determined, and concerns have been raised on the effects of tolvaptan on TKV and whether they might become negligible over several years of treatment [38]. The potential benefits of early diagnosis and treatment also need to be weighed against the potential negative effects, such as increased anxiety, recurrent visits to the physician, and insurance-related issues.

Before prescribing tolvaptan in cases of pediatric ADPKD, genetic information should be acquired, TKV should be determined, and complete assessment should

be performed; additionally, patients' education and long-term follow-up on side effects are necessary (shown in Fig. 1). Overall, although the use of tolvaptan requires careful consideration and balancing of the benefits and risks, tolvaptan is a valuable treatment option to delay the progression of ADPKD in patients at risk of or showing signs of rapidly progressing disease. Data from the global ADPKD projects will help improve our understanding of disease progression from early disease stages [54]. The first trial on the treatment of pediatric ADPKD using tolvaptan is currently underway, which is expected to yield encouraging results. More real-world studies focused on patient selection criteria, dosing, pharmacology, adverse effects, and monitoring are required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by grants from the Key Research and Development Plan of Zhejiang Province (No. 2019C03028 and 2021C03079).

Author Contributions

All the authors have contributions to this review. The main contents of this review were analyzed and written by Fei Liu, assisted by Chunyue Feng, Huijun shen, Haidong Fu, and Jianhua Mao provided guidance and revision.

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