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# Tolvaptan: a possible preemptive treatment option in children with autosomal dominant polycystic kidney disease?

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Tolvaptan is a highly selective vasopressin receptor 2 antagonist that regulates cyclic adenosine monophosphate levels to inhibit both epithelial cell proliferation and chloride ion excretion, two mechanisms known to induce cyst expansion in autosomal dominant polycystic kidney disease (ADPKD). Tolvaptan is currently the preferred treatment of rapidly progressive disease ADPKD in adult patients; however, since cyst formation in ADPKD begins early in life, (frequently in utero), and significant disease progression with cyst expansion occurs in the first decade, tolvaptan may be advantageous as a preemptive treatment in children with ADPKD. Tolvaptan has already been used to successfully treat refractory edema or hyponatremia in children; this literature review provides insight into the biochemical basis of its action to contextualize its use in the pediatric population.

**Keywords:** Child; Polycystic kidney, autosomal dominant; Tolvaptan

## Introduction

Tolvaptan is a highly selective vasopressin receptor 2 (V2R) antagonist that acts by regulating cyclic adenosine monophosphate (cAMP) levels to inhibit both epithelial cell proliferation and chloride ion excretion, two mechanisms responsible for inducing cyst expansion in autosomal dominant polycystic kidney disease (ADPKD) [1,2]. The TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) trial [3] and the REPRISE (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD) trial [4] concluded that tolvaptan delays the increase in total kidney volume (TKV) and the decline in renal function in adult patients with ADPKD. Therefore, tolvaptan is currently the preferred treatment option for rapidly progressing ADPKD in adult patients in Japan, Canada, the EU, the USA, and Korea. Clinicians consider ADPKD to be essentially an adult-onset disease because serum creatinine levels typically remain within the normal range during childhood, and symptoms of end-stage kidney disease (ESKD) typically develop only in the fifth or sixth decade. However, cyst formation in ADPKD begins early in life, frequently in utero; notably, significant disease progression with renal cyst formation and expansion occurs in the first decade. Therefore, ADPKD cannot be isolated to adults only. This review tries to find out whether tolvaptan can be the option of preemptive treatment in children with ADPKD.

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## Tolvaptan in adult patients with ADPKD

The polycystin complex (polycystin-1, polycystin-2, and fibrocystin/polyductin) is located in the primary cilia as membrane-associated proteins; it translates mechanical stimulation of the cilia into calcium entry, which triggers calcium-induced calcium release from the endoplasmic reticulum [2]. In ADPKD, polycystin levels are reduced below a critical threshold which disturbs the intracellular calcium homeostasis and enhances cAMP accumulation by increasing adenylyl cyclase type 6 (AC6) activity. This further stimulates epithelial cell proliferation activated by mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling and chloride-driven fluid excretion driven by the cystic fibrosis transmembrane conductance regulator (CFTR) and ultimately induces cyst expansion in ADPKD [2]. In addition, arginine vasopressin acts by binding to V2R, which stimulates AC6 as a GS protein-coupled receptor that increases intracellular cAMP levels [1]. In this regard, tolvaptan acts as a highly selective V2R antagonist that regulates cAMP levels to inhibit both epithelial cell proliferation by MAPK/ERK signaling and chloride-driven fluid excretion by CFTR in ADPKD (Fig. 1).

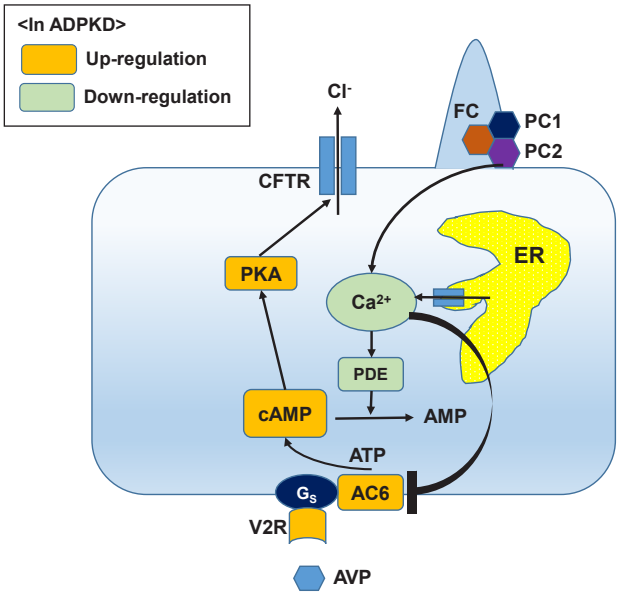


**Fig. 1.** Schematic pathway of chloride-driven fluid excretion in polycystic kidney disease. ADPKD, autosomal dominant polycystic kidney disease; FC, fibrocystin; PC1, polycystin-1; PC2, polycystin-2; ER, endoplasmic reticulum; CFTR, cystic fibrosis transmembrane conductance regulator; PKA, protein kinase A; PDE, phosphodiesterase; AMP, adenosine monophosphate; cAMP, cyclic AMP; ATP, adenosine triphosphate; AC6, adenylyl cyclase type 6; V2R, vasopressin receptor 2; AVP, arginine vasopressin.

In 2012, Torres et al. [3] published the results of a three-year, phase-III, multicenter, double-blind, placebo-control study on 1445 ADPKD patients (aged 18–50 years) with a TKV of >750 mL and an estimated creatinine clearance of ≥60 mL/min. The tolvaptan treatment group demonstrated only a 2.8% increase in the TKV compared to 5.51% in the placebo treatment group, showing a significant treatment effect. Likewise, the reduction in renal function, as evaluated using reciprocal serum creatinine, was significantly delayed in the treatment group as compared to the placebo treatment (−2.61 vs. −3.81; $P<0.001$). These results provided a cornerstone for the selection of tolvaptan as a treatment for ADPKD (TEMPO 3:4 trial) [3]. However, there was a significant increase of adverse events in the patients who received tolvaptan. These adverse events were related to elevation of liver-enzyme levels and increased aquaresis such as polyuria, thirst, nocturia, and polydipsia [3].

Five years later, Torres et al. [4] conducted follow-up studies of the TEMPO 3:4 trial and published them as the REPRISE trial. The trial included a total of 1,370 patients with ADPKD aged either 18–55 years with an estimated glomerular filtration rate (eGFR) of 25–65 mL/min/1.73 $m^2$ or 56–65 years with an eGFR of 25–44 mL/min/1.73 $m^2$. The patients were subjected to a 1:1 random allocation with tolvaptan and placebo and observed for 12 months. This study was more advanced than the TEMPO 3:4 trial. The authors concluded tolvaptan led to a significant delay in the rate of decrease in renal function, and long-term treatment was safe, which was corroborated via additional extended study [5].

In 2021, comparative results of the REPRISE trial and the aforementioned open-label extension trial were published. A post hoc analysis was done which retrospectively investigated patients with very low residual renal function (eGFR, 15–29 mL/min/1.73 $m^2$), which reported that both the extension and initiation of tolvaptan treatment were significantly effective in subjects with very low renal function. Therefore, tolvaptan offers beneficial therapeutic effects in patients diagnosed with ADPKD regardless of residual kidney function [6].

A pooled longitudinal analysis published in 2022 analyzed the results of eight clinical studies using tolvaptan and five clinical studies without tolvaptan, drawing attention to verifying the effectiveness of tolvaptan [7]. Over a long follow-up period of 5.5 years, tolvaptan was found to delay renal function loss by an eGFR of 1.01 mL/min/1.73 $m^2$ compared to the standard of the case group. Overall, the therapeutic effect of tolvaptan has been

extensively studied, which forms the basis of several treatment guidelines for its use in ADPKD [8-12].

## Tolvaptan: experiences with pediatric use

Tolvaptan has been widely used in children for various indications other than ADPKD, such as severe edema and hyponatremia [13-22]. The first account of tolvaptan use in children is from Japan in 2014–an 8 years old girl diagnosed with steroid-resistant nephrotic syndrome received tolvaptan for one week for severe edema. This led to a significant increase in the urine volume without a concomitant increase in urine protein [13]. Since then, various cases have reported the effectiveness and safety of tolvaptan in pediatric patients in conditions involving hyponatremia, such as the syndrome of inappropriate antidiuretic hormone, for regulating body fluids in congestive heart failure, or after open heart surgery [14-20]. In a prospective study involving tolvaptan use in pediatric patients with nephrotic syndrome and severe edema, Meena et al. [21] reported a significant increase in urine volume by co-administering tolvaptan for 48 hours in patients who did not respond adequately to 48 hours of furosemide treatment.

In 2022, Piffer et al. [22] conducted a systematic literature review of 26 papers that reported vaptan-based treatment experiences for edema and hyponatremia published since 2008. The review included 115 pediatric patients with vaptan-based treatment, of which 63 were treated for hyponatremia and 52 for edema. Although vaptan-based treatment did not show superior results to conventional treatments for edema and hyponatremia, it showed substantial therapeutic effects, and only a few side effects, highlighting its safety in children.

## Possible preemptive use of tolvaptan in pediatric ADPKD patients

ADPKD is often recognized as a disease confined to adults owing to the perception that most patients are asymptomatic during childhood. However, the following facts suggest that it is necessary to recognize that ADPKD requires early diagnosis and treatment in children. First, children with ADPKD are likely to have an overestimation of eGFR because of glomerular hyperfiltration for a considerable period. Therefore, the eGFR may not be an appropriate indicator of the progression of ADPKD during childhood. Second, the formation and expansion of renal cysts in ADPKD patients are already underway from the fetal period; also, the associated kidney damage starts from childhood. Therefore, TKV may not be the optimum prognostic indicator of ADPKD during childhood. Third, about 2%–5% of all ADPKD patients have severe clinical findings comparable to autosomal recessive polycystic kidney disease. Various clinical symptoms, such as frequency, polyuria, hematuria, urinary tract infection, renal stones, abdominal pain, hypertension, and proteinuria may be evident, but pediatric guidelines for managing them have not yet been established. Therefore, conclusive efforts are warranted to integrate pediatric ADPKD patients, who are currently excluded, into the purview of treatment using tolvaptan [23-25].

There are a few additional considerations. Since many patients dropped out of the TEMPO 3:4 trial due to drug side effects, clinicians should be cautious of the possible side effects of tolvaptan use. Children are more vulnerable to dehydration or electrolyte imbalance caused by the aquaretic effects of tolvaptan; likewise, hepatotoxicity is also a known side effect [26]. Therefore, appropriate counter-measures and monitoring should also be applied with tolvaptan use. Furthermore, not all patients with ADPKD progress to ESKD, so patient screening is extremely important. Currently, TKV is used as a valid predictive indicator in adult patients with rapidly progressive disease; however, the same cannot be applied to children. Thus, it is important to discover new biological markers that can be used as valid predictive indicators [27].

To date, tolvaptan has been rarely used in children. In 2017, Gilbert et al. [28] first reported tolvaptan use in a newborn with ADPKD with a family history of the disease. The patient developed pulmonary dysplasia due to huge kidneys at birth along with obstruction of the inferior vena cava, showing symptoms comparable to ADPKD. The infant was treated with 0.5 mg/kg/day of tolvaptan from 3 months of age which was increased to 1 mg/kg/day; the infant showed normal growth up to 12 months of age.

In 2021, a study published a post hoc analysis of the adolescents and young adults (aged 18–24 years) of the TEMPO 3:4 trial conducted in 2012 [29]. Of a total of 1,445 patients aged 18–50 years, 63 patients met the age criteria; 50 out of 63 patients were identified as having rapid progression (22 placebo group patients and 28 in the tolvaptan group). The authors noted that the change in TKV in the tolvaptan group was significantly lower than that of the placebo group, suggesting the possibility of using tolvaptan even in the younger age group.

In 2019, a multicenter, prospective study was conducted



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**Table 1.** Recommendations for follow-up in children with ADPKD

| Follow-up | Recommendation |
|---|---|
| Regular follow-up (every 1–3 yr; without HTN or proteinuria) | · Measure BP and urine protein excretion (at least once a year)<br>· Perform ABPM at least once from age 5 yr<br>· Consider repeated ultrasound depending on the clinical course and the age of the patient<br>· Enquire about further at-risk siblings<br>· Address psychosocial issues<br>· Advise lifestyle modification (physical activity, maintenance of normal weight, low-salt diet, high water intake, avoidance of excessive protein intake) |
| Advanced follow-up (with HTN or proteinuria) | · Perform ABPM to confirm HTN<br>· Use RAAS inhibitors as 1st line therapy and follow-up (target BP: below 75th percentile or <125/72 mmHg if age >16 yr)<br>· Screen for end-organ damage (eye, heart) |

ADPKD, autosomal dominant polycystic kidney disease; HTN, hypertension; BP, blood pressure; ABPM, ambulatory blood pressure monitoring; RAAS, renin-angiotensin-aldosterone system.

by Schaefer et al. [30] to evaluate the effects and side effects of tolvaptan in children with ADPKD. The study consisted of two types: phase A was planned as a 1-year, randomized, double-blinded, placebo-controlled multicenter trial, and phase B as a 2-year open-label extension trial. The study included pediatric ADPKD patients aged 4–17 years (weight ≥20 kg; eGFR ≥60 mL/min/1.73 $m^2$) diagnosed with ADPKD based on family history or genetic testing; at least 10 cysts (>4 for patients under 12 years of age) were identified for inclusion in the study.

In 2023, Mekahli et al. [31] published the results of this prospective study. A total of 91 patients participated in the study (48 in the tolvaptan group and 43 in the placebo group). The authors noted that the spot urine osmolality and specific gravity measured 1 week after drug administration were significantly lower in the tolvaptan group, confirming the efficacy of tolvaptan in pediatric patients. However, unfortunately, there was no significant difference in the changes in height-adjusted TKV over the year. It was reported that aquaretic adverse events were more common in the tolvaptan group compared to the placebo group (65% vs. 16%, respectively) and there were no elevated transaminases or drug-induced liver injuries [31].

## Monitoring in children with ADPKD (before the tolvaptan era)

Certain issues need to be addressed before clinically using tolvaptan in pediatric ADPKD patients. At present, it is advisable to refer to the results of studies that have been published recently while following the international consensus statement [32]. First, a child with renal cysts and a family history of ADPKD or diagnosed with ADPKD through genetic testing must be checked for related symptoms, such as urinary tract infection, renal stones, hematuria, and abdominal pain. Blood pressure monitoring and urine protein excretion should be regularly performed every 1–3 years. In addition, it is important to ensure other siblings are tested, but general tests for extrarenal manifestations are not recommended. Patients must be educated on sufficient water intake, low-salt diet, exercise, smoking cessation, and weight control to improve lifestyle habits. Patients with confirmed hypertension or proteinuria should undergo regular ambulatory blood pressure monitoring and be strictly managed using renin-angiotensin-aldosterone inhibitor as the first-line therapy. Lastly, it is important to check for end-organ damage, including eye and heart (Table 1) [24,32].

## Conclusion

Tolvaptan is a widely used treatment option to improve the prognosis of adult ADPKD patients, but there are several problems precluding its use in children. It is also true that the experience with tolvaptan use in children has been generally favorable without leading to significant hepatotoxicity compared to adults. Therefore, future studies must explore the preemptive use of tolvaptan in pediatric ADPKD patients.

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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## Author contributions

All the work was done by HSB and MHC.

## References

1. Olesen ET, Fenton RA. Aquaporin 2 regulation: implications for water balance and polycystic kidney diseases. Nat Rev Nephrol 2021;17:765-81.
2. Torres VE. Role of vasopressin antagonists. Clin J Am Soc Nephrol 2008;3:1212-8.
3. Torres VE, Chapman AB, Desvuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012;367:2407-18.
4. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med 2017;377:1930-42.
5. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Lee J, et al. Multicenter study of long-term safety of tolvaptan in later-stage autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 2020;16:48-58.
6. Torres VE, Gansevoort RT, Perrone RD, Chapman AB, Ouyang J, Lee J, et al. Tolvaptan in ADPKD patients with very low kidney function. Kidney Int Rep 2021;6:2171-8.
7. Zhou X, Davenport E, Ouyang J, Hoke ME, Garbinsky D, Agarwal I, et al. Pooled data analysis of the long-term treatment effects of tolvaptan in ADPKD. Kidney Int Rep 2022;7:1037-48.
8. Chebib FT, Perrone RD, Chapman AB, Dahl NK, Harris PC, Mrug M, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. J Am Soc Nephrol 2018;29:2458-70.
9. Muller RU, Messchendorp AL, Birn H, Capasso G, Cornec-Le Gall E, Devuyst O, et al. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. Nephrol Dial Transplant 2022;37:825-39.
10. Gkekas E, Tang TY, Green A, Davidson H, Fraser R, Sayer JA, et al. Outcomes from the Northeast England cohort of autosomal dominant polycystic kidney disease (ADPKD) patients on tolvaptan. Front Nephrol 2022;2:984165.
11. Kataoka H, Shimada Y, Kimura T, Nishio S, Nakatani S, Mochizuki T, et al. Public support for patients with intractable diseases in Japan: impact on clinical indicators from nationwide registries in patients with autosomal dominant polycystic kidney disease. Clin Exp Nephrol 2023;27:809-18.
12. Gkika V, Louka M, Tsagkatakis M, Tsirpanlis G. The efficacy, the treatment response and the aquaretic effects of a three-year tolvaptan regimen in polycystic kidney disease patients. Clin Pract 2023;13:1035-42.
13. Shimizu M, Ishikawa S, Yachi Y, Muraoka M, Tasaki Y, Iwasaki H, et al. Tolvaptan therapy for massive edema in a patient with nephrotic syndrome. Pediatr Nephrol 2014;29:915-7.
14. Marx-Berger D, Milford DV, Bandhakavi M, Van't Hoff W, Kleta R, Dattani M, et al. Tolvaptan is successful in treating inappropriate antidiuretic hormone secretion in infants. Acta Paediatr 2016;105:e334-7.
15. Higashi K, Murakami T, Ishikawa Y, Itoi T, Ohuchi H, Kodama Y, et al. Efficacy and safety of tolvaptan for pediatric patients with congestive heart failure. Multicenter survey in the working group of the Japanese Society of PEdiatric Circulation and Hemodynamics (J-SPECH). Int J Cardiol 2016;205:37-42.
16. Katayama Y, Ozawa T, Shiono N, Masuhara H, Fujii T, Watanabe Y. Safety and effectiveness of tolvaptan for fluid management after pediatric cardiovascular surgery. Gen Thorac Cardiovasc Surg 2017;65:622-6.
17. Tuli G, Tessaris D, Einaudi S, De Sanctis L, Matarazzo P. Tolvaptan treatment in children with chronic hyponatremia due to inappropriate antidiuretic hormone secretion: a report of three cases. J Clin Res Pediatr Endocrinol 2017;9:288-92.
18. Koksoy AY, Kurtul M, Ozsahin AK, Cayci FS, Tayfun M, Bayrakci US. Tolvaptan use to treat SIADH in a child. J Pediatr Pharmacol Ther 2018;23:494-8.
19. Kerling A, Toka O, Ruffer A, Muller H, Habash S, Weiss C, et al. First experience with tolvaptan for the treatment of neonates and infants with capillary leak syndrome after cardiac surgery. BMC Pediatr 2019;19:57.
20. Delbet JD, Parmentier C, Ulinski T. Tolvaptan therapy to treat severe hyponatremia in pediatric nephrotic syndrome. Pediatr Nephrol 2020;35:1347-50.
21. Meena J, Hari P, Sinha A, Bagga A. Efficacy and safety of combination therapy with tolvaptan and furosemide in children with nephrotic syndrome and refractory edema: a prospective interventional study. Indian J Pediatr 2022;89:699-705.
22. Piffer A, Bianchetti MG, Leoni-Foglia C, Simonetti GD, Milani GP, Lava SA. Vaptans for oedematous and hyponatraemic disorders in childhood: a systematic literature review. Br J Clin Pharmacol



https://doi.org/10.3339/ckd.23.021

2022;88:4474-80.
23. Hartung EA. Tolvaptan for autosomal dominant polycystic kidney disease in children: why, who, and when? Clin J Am Soc Nephrol 2023;18:11-3.
24. Gimpel C, Bergmann C, Mekahli D. The wind of change in the management of autosomal dominant polycystic kidney disease in childhood. Pediatr Nephrol 2022;37:473-87.
25. De Rechter S, Breysem L, Mekahli D. Is autosomal dominant polycystic kidney disease becoming a pediatric disorder? Front Pediatr 2017;5:272.
26. Alpers DH, Lewis JH, Hunt CM, Freston JW, Torres VE, Li H, et al. Clinical pattern of tolvaptan-associated liver injury in trial participants with autosomal dominant polycystic kidney disease (ADPKD): an analysis of pivotal clinical trials. Am J Kidney Dis 2023;81:281-93.
27. Janssens P, Weydert C, De Rechter S, Wissing KM, Liebau MC, Mekahli D. Expanding the role of vasopressin antagonism in polycystic kidney diseases: from adults to children? Pediatr Nephrol 2018;33:395-408.
28. Gilbert RD, Evans H, Olalekan K, Nagra A, Haq MR, Griffiths M. Tolvaptan treatment for severe neonatal autosomal-dominant polycystic kidney disease. Pediatr Nephrol 2017;32:893-6.
29. Raina R, Chakraborty R, DeCoy ME, Kline T. Autosomal-dominant polycystic kidney disease: tolvaptan use in adolescents and young adults with rapid progression. Pediatr Res 2021;89:894-9.
30. Schaefer F, Mekahli D, Emma F, Gilbert RD, Bockenhauer D, Cadnapaphornchai MA, et al. Tolvaptan use in children and adolescents with autosomal dominant polycystic kidney disease: rationale and design of a two-part, randomized, double-blind, placebo-controlled trial. Eur J Pediatr 2019;178:1013-21.
31. Mekahli D, Guay-Woodford LM, Cadnapaphornchai MA, Greenbaum LA, Litwin M, Seeman T, et al. Tolvaptan for children and adolescents with autosomal dominant polycystic kidney disease: randomized controlled trial. Clin J Am Soc Nephrol 2023;18:36-46.
32. Gimpel C, Bergmann C, Bockenhauer D, Breysem L, Cadnapaphornchai MA, Cetiner M, et al. International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. Nat Rev Nephrol 2019;15:713-26.