Original Article

Low-dose tolvaptan to control disease progression in Chinese patients with autosomal dominant polycystic kidney disease: a retrospective cohort study

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Background: Tolvaptan has been shown to be effective in the treatment of autosomal dominant polycystic kidney disease (ADPKD). However, there is limited evidence regarding optimal dosing and its application within the Chinese population. In this study, we aimed to determine whether a lower tolvaptan dose could effectively control ADPKD in Chinese patients.

Methods: This retrospective, single-center cohort study was conducted in a real-world setting and included all patients newly diagnosed with rapidly progressive ADPKD who initiated tolvaptan treatment and maintained it for at least 12 months. Data were collected at baseline and at 1, 2, 4, 8, and 12 months after treatment initiation. Patients began with morning/evening tolvaptan doses of 7.5 mg/7.5 mg, and the dose was subsequently adjusted based on effectiveness and tolerability. The patients were categorized by baseline estimated glomerular filtration rate (eGFR) and final daily tolvaptan dose. Changes in eGFR and other key physiological indicators after treatment were compared within each group.

Results: The study included 43 patients with ADPKD, of whom 20 were female, with a median age of 34.3 years (range, 16–85 years). At 12 months, eGFR improved by 5.48 mL/min/1.73 m^2 [95% confidence interval (CI): 2.68–8.29] (P<0.001) compared to baseline. Significant improvements were observed in patients with baseline eGFR levels of 30–59, 60–89, and ≥90 mL/min/1.73 m^2 (P=0.007, 0.045, and 0.02, respectively), as well as in medium and high dose groups (P=0.002 and 0.02, respectively). At 12 months, the annual height-adjusted total kidney volume (HtTKV) growth slope decreased by −0.17 %/year (95% CI: −0.33 to −0.01) (P=0.04). Significant decreases were observed in patients with an eGFR of 30–59 mL/min/1.73 m^2 (P=0.008) and in the medium dose group (P=0.03). Thirst was reported in 22 (51.2%) patients, all of whom experienced mild symptoms. No liver-associated adverse events were noted.

Conclusions: Tolvaptan is well tolerated at low initial doses in Chinese patients with ADPKD. Significant improvements in eGFR and reduced HtTKV growth were observed in the overall population and across various baseline eGFR and final dose groups.

Keywords: Autosomal dominant polycystic kidney disease (ADPKD); tolvaptan; daily dose

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease, with a global prevalence of approximately 1/1,000–1/2,500. In China, the prevalence of ADPKD is 1/400–1/1,000, with an estimated 1.4–3.5 million patients (1-3). ADPKD is characterized by the development of renal cysts, which gradually increase and enlarge with age and compress normal kidney tissue, leading to the destruction of kidney structure and function (3-5). Most patients with ADPKD develop bilateral renal cysts in adulthood (6,7), approximately 98% of the patients start developing symptoms after the age of 15 years (8); and about 50% of ADPKD patients progress to end-stage kidney disease (ESKD) by the age of 60 years; in fact, ADPKD is the fourth leading cause of ESKD (9,10). Patients with ADPKD often experience complications such as chronic pain, gross hematuria, cyst infection, and kidney stones, which seriously impact the quality of life of patients (1). ADPKD can also cause extrarenal lesions such as hepatic cysts, heart valve disease, and intracranial aneurysms. Therefore, ADPKD is also a systemic disease with multi-organ involvement (1).

The antidiuretic hormone arginine vasopressin and its secondary messenger 3',5'-cyclic adenosine monophosphate are promoters of cell proliferation and luminal fluid secretion in renal cysts (11,12). Inhibition of vasopressin release (13,14) by large water intake, vasopressin gene elimination, and vasopressin V2 receptor blockade reduces cyst burden and protects kidney function in patients with ADPKD (15-19). The vasopressin V2 receptor antagonist tolvaptan is the first and only disease-modifying drug shown to slow estimated glomerular filtration rate (eGFR) decline in high-risk ADPKD patients. It is now approved in many countries as the standard of care for these individuals. A number of studies have shown that the vasopressin V2 receptor antagonist tolvaptan can reduce the annual kidney volume (TKV) growth slope and delay the growth of total TKV, the decline in eGFR, and the time to dialysis or renal transplantation in patients with ADPKD (20-25). Furthermore, tolvaptan was observed to reduce the incidence of complications, including renal pain, urinary tract infection, hematuria, and hypertension (15).

While effective, the use of tolvaptan presents potential challenges. The most common barrier to tolvaptan therapy is the concern over intolerability due to aquaretic side effects, followed by the financial burden on patients (26,27). The use of tolvaptan is associated with several side effects, with the most common being aquaretic symptoms such as thirst, polydipsia, polyuria, nocturia, and pollakiuria (21,22). Other side effects may include acute liver toxicity, acute kidney injury, and gout (21-23). The rates of adverse events (AEs), including polyuria, are shown to be dose-dependent in North American and Japanese patients (25). Tolvaptan is an expensive medication, and its long-term cost-effectiveness has yet to be established. Given these potential drawbacks, it is crucial to carefully select patients and determine appropriate dosing to ensure a favorable benefit-to-risk ratio.

Tolvaptan for ADPKD is available in three dosing regimens (45/15, 60/30, and 90/30 mg), administered twice daily (28). However, the minimum level of blockade necessary to achieve treatment benefits in individual patients remains unclear. Initiating treatment with lower doses (e.g., 15/15 and 30/15 mg) could reduce early discontinuation, enhance tolerability during titration, and facilitate treatment for patients who are highly sensitive to tolvaptan and may otherwise be unable to tolerate it (29). This is particularly relevant for Asians, who are generally smaller in size than Westerners and may have difficulty withstanding a dose of 90/30 mg (30).

The international consensus of the Working Group on Inherited Kidney Disorders recommends that patients treated with tolvaptan should have an eGFR of ≥25 mL/min/1.73 m^2 based on the TEMEPO 3:4 and the

Highlight box

Key findings

- Tolvaptan is well tolerated at lower initial doses in Chinese patients with autosomal dominant polycystic kidney disease (ADPKD).
- In patients with final daily tolvaptan dose of >15–30 mg and >30–60 mg, the estimated glomerular filtration rate (eGFR) significantly improved at 12 months.
- In patients with a final daily tolvaptan dose of >15–30 mg, the annual height-adjusted total kidney volume (HtTKV) growth slope significantly decreased at 12 months.

What is known and what is new?

- Tolvaptan is effective in reducing the annual HtTKV growth slope, slowing the decline in eGFR, as well as extending the time to dialysis or renal transplantation in patients with ADPKD.
- Low-dose tolvaptan treatment can achieve significant clinical benefits in Chinese patients.

What is the implication, and what should change now?

- Clinical guidelines for tolvaptan dosing in ADPKD should be re-evaluated to include lower starting doses, particularly for the Chinese population, to enhance tolerability and efficacy.

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REPRISE trial (22,23,28). A low eGFR was reported as the most frequent contraindication for initiating tolvaptan (27), as there is a lack of evidence for this population and the potential benefits of delaying dialysis are considered minimal due to already advanced renal damage (28,29). However, clinical experience shows that patients for whom tolvaptan treatment is not recommended commonly exhibit visible hematuria and repeated cyst rupture. In severe cases, the kidney function is further damaged, and the risk of renal failure, cyst infection, and pain is accelerated; tolvaptan might be considered in such patients. As the only disease-modifying drug for ADPKD to date, investigating its suitability for patients with low eGFR could provide valuable evidence to inform clinical decisions.

Evidence gaps remain in several key areas regarding tolvaptan, particularly dosing, its use in patients with low eGFR, and its application within the Chinese context. Despite the establishment of guidelines and expert consensus for tolvaptan treatment of ADPKD in China, there is a lack of clinical studies specifically evaluating its effectiveness and safety in Chinese patients. Therefore, this study aimed to assess the effectiveness and safety of tolvaptan in a real-world cohort in China. Specifically, patients were stratified into dosing and eGFR groups to evaluate the effects of low-dose tolvaptan on achieving disease stability and delaying disease progression in patients with low eGFR who had a strong willingness to receive tolvaptan treatment. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-448/rc).

Methods

Study design

This study included all patients who were newly diagnosed with rapidly progressive ADPKD in our center from 1 October 2021 to 30 October 2022, agreed to voluntarily initiate tolvaptan treatment, and continued treatment for at least 12 months. Data were retrospectively collected from the electronic medical records. According to guideline recommendations, patients initiating tolvaptan treatment were required to visit the hospital monthly for dose adjustments and liver function monitoring. Data were collected at baseline (0 months) and at 1, 2, 4, 8, and 12 months after treatment initiation for analysis. Subgroups were established based on two criteria: baseline eGFR and final daily tolvaptan dose. Patients were categorized into 5 groups according to their baseline eGFR levels: ≥90, 60–89, 30–59, 15–29, and 0–14 mL/min/1.73 m^2. Additionally, patients were categorized into 3 groups according to the final daily tolvaptan dose: low dose (15 mg), medium dose (>15 and ≤30 mg), and high dose (>30 and ≤60 mg).

The inclusion criteria included normal urine and normal liver function. Pregnant women, patients under 15 years of age, those with urinary obstruction, and those with abnormal liver function were excluded. The ultrasound diagnostic criteria for ADPKD were ≥3 single/bilateral renal cysts in patients aged 15–39 years, ≥2 cysts on each side in patients aged 40–59 years, and ≥4 renal cysts on each side in patients aged ≥60 years. The presence of ≥10 renal cysts in total was used as the diagnostic criterion for ADPKD based on computed tomography (CT) or magnetic resonance imaging (MRI).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of China-Japan Friendship Hospital (No. 2023-KY-329) and individual consent for this retrospective analysis was waived.

Treatment regimen

All patients received tolvaptan with dose escalation. The initial dose was morning/evening doses of 7.5 mg/7.5 mg, and the treatment dose was adjusted monthly according to the effectiveness and tolerability of the patients and increased to 15 mg/7.5 mg, 30 mg/7.5 mg, 15 mg/15 mg, 22.5 mg/7.5 mg, 22.5 mg/15 mg, 30 mg/15 mg, and 45 mg/15 mg. The maximum daily dose was 60 mg. The patients took the medication at 8:00 and 16:00 to ensure that the peak urination ended before bedtime and that the impact on sleep was minimized. All patients were treated for a total of 12 months. During the treatment period, CYP3A inhibitors and diuretics were discontinued, and the female patients were strongly recommended to use contraception. Patients of different ages and weights were given different doses.

Study endpoints

The primary study aim was to assess the effectiveness of lower tolvaptan doses in controlling the progression of ADPKD. Serum levels of creatinine (Cr) and uric acid (UA), as well as eGFR, are important parameters of kidney function. Therefore, the primary study endpoint was a progression of nephropathy determined by evaluating the trend in eGFR change during treatment in groups

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categorized according to baseline eGFR and in those categorized according to the tolvaptan dose. Key secondary endpoints were the trends of change in serum Cr, UA, and Na^+ levels; the annual growth slope of height-corrected TKV (HtTKV) in groups categorized according to baseline eGFR and in those categorized according to the tolvaptan dose; and patient HtTKV and TKV. All study endpoints were evaluated at 0, 1, 2, 4, 8, and 12 months, except for the annual TKV growth slope and TKV, which were assessed at 0, 4, 8, and 12 months.

Study assessments

Ultrasonography was evaluated by sonographers with more than 3 years of work experience. The patient was placed in the supine and lateral positions, and the morphology and structure of the kidney were examined using the abdominal convex-array probe. The section with the maximum longitudinal renal axis was identified to measure the long diameter along the maximum longitudinal axis and the renal width and thickness in the horizontal cross-section of the renal hilum. Next, the size of the largest cyst and the cyst with bleeding were measured in both kidneys, and their locations were described. Each patient was examined by the same sonographer using the same technique to ensure data consistency. In the present study, all imaging evaluations were performed using ultrasonography for 2 reasons. To maintain data consistency, ultrasound detection was uniformly used in all patients. Second, ultrasound detection is a relatively economical and safe method and is more acceptable to patients.

eGFR was calculated based on serum Cr using the Chronic Kidney Disease Epidemiology Collaboration equation (28,31). TKV, the main indicator to evaluate ADPKD progression, was determined based on imaging methods such as MRI. For patients younger than 25 years, image stereometry was used to accurately measure TKV. For patients aged ≥25 years, TKV was estimated using a web calculator provided by the Mayo Clinic after obtaining the maximum length, width, and thickness of both kidneys using ultrasound (32).

Liver function was evaluated at weeks 2 and 4 and monthly thereafter. The treatment was discontinued in patients with increasing liver aminotransferase levels to more than 3 times the upper limit of the normal range, in those with increasing total bilirubin levels to more than 2 times the upper limit of the normal range, and in those with severe liver-related AEs.

Statistical analysis

Qualitative data were presented as the frequency. Normally distributed quantitative data were presented as means ± standard deviation, while non-normally distributed quantitative data were presented as medians (25th–75th percentiles). For each endpoint, comparisons between the 12-month and 0-month time points were conducted using paired *t*-tests. Differences across various time points were compared using repeated measures analysis of variance (ANOVA). Effect sizes were estimated using generalized eta squared. Spearman correlation analysis was conducted to assess correlations. Analyses were performed on the respective subgroups. All statistical analyses were performed using R (version 4.1.2). All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

Study population

The study population included 43 patients with ADPKD, including 20 female patients, with a median age of 34.29 years (range, 16–85 years). The baseline patient characteristics are shown in *Table 1*. The distribution of patients across baseline eGFR groups was as follows: ≥90 mL/min/1.73 m^2 (n=7), 60–89 mL/min/1.73 m^2 (n=8), 30–59 mL/min/1.73 m^2 (n=13), 15–29 mL/min/1.73 m^2 (n=5), and 0–14 mL/min/1.73 m^2 (n=10). The distribution of patients by final daily tolvaptan dose was: 15 mg (n=14), 15–30 mg (n=22), and 30–60 mg (n=7).

Changes in eGFR over time

At 12 months, eGFR improved by 5.48 mL/min/1.73 m^2 [95% confidence interval (CI): 2.68–8.29] (P<0.001) compared to baseline, and the mean eGFR levels across different time points were significantly different (P<0.001). As shown in *Table 2*, significant improvements in eGFR at 12 months compared to baseline were observed in patients with baseline eGFR levels of 30–59, 60–89, and ≥90 mL/min/1.73 m^2 (P=0.007, 0.045, and 0.02, respectively). The mean eGFR levels across different time points were significantly different only in patients with baseline eGFR levels of 30–59 mL/min/1.73 m^2 (P=0.03; see *Table 2* and *Figure 1*). Significant improvements in eGFR at 12 months compared to baseline were observed in patients in the medium and high dose groups (P=0.002 and 0.02, respectively). The mean eGFR levels across different time

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Table 1 Baseline patient characteristics

Characteristic	Overall (n=43)	Baseline eGFR (mL/min/1.73 m^2)				
		≥90 (n=7)	60–89 (n=8)	30–59 (n=13)	15–29 (n=5)	0–14 (n=10)
Female (n)	20	3	3	5	3	6
Average age (years)	47.58	34.29	45.38	50.31	51.80	53.00
Average body weight (kg)	69.78	68.16	72.44	67.73	69.60	71.55
Average serum UA (μmol/L)	400.07	372.03	409.63	409.37	360.58	406.89
Average eGFR (mL/min/1.73 m^2)	48.15	114.13	67.91	43.31	17.95	7.56
Average serum Cr (μmol/L)	260.02	66.40	102.24	150.02	304.34	642.60
Average final daily tolvaptan dose (mg)	26.34	23.57	31.88	30.58	27.00	18.00
Average ALT (IU/L)	23.28	31.44	23.25	26.38	19.40	15.50
Average AST (IU/L)	21.69	23.57	27.25	23.54	16.94	15.90
Average TBIL (μmol/L)	13.80	13.65	20.4	12.17	9.08	6.54
Average K^+ (mmol/L)	4.40	4.24	4.07	4.17	4.88	4.79
Average Na^+ (mmol/L)	140.61	140.07	141.34	140.98	141.72	139.23
Average TKV (mL)	3,443.48	959.03	1,953.23	2,524.10	3,814.23	5,596.50
Kidney stones (n)	35	5	8	12	4	6
Gross hematuria (n)	26	2	3	7	5	9

UA, uric acid; eGFR, estimated glomerular filtration rate; Cr, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; TKV, total kidney volume.

points were significantly different only in the high dose group (P=0.04; see *Table 2* and *Figure 1*).

Changes in secondary endpoints over time

At 12 months, serum UA levels decreased by −39.90 μmol/L (95% CI: −77.22 to −2.59) compared to baseline (P=0.04). The annual HtTKV growth slope decreased by −0.17 %/year (95% CI: −0.33 to −0.01) (P=0.04). No significant changes were observed for serum Cr level, serum Na^+ levels, TKV, or HtTKV.

Table 3 summarizes the changes in secondary endpoints among groups categorized by baseline eGFR. In patients with a baseline eGFR of 30–59 mL/min/1.73 m^2, the serum Cr level was significantly lower at 12 months (P<0.001), and mean Cr levels across different time points were significantly different (P=0.005). Serum UA levels did not show significant differences among the evaluated time points in any of the eGFR groups. No significant differences were observed for serum Na^+ levels at 12 months; however, mean Na^+ levels across different time points were significantly different in patients with baseline eGFR levels of 0–14 and 30–59 mL/min/1.73 m^2 (P=0.020 and 0.005, respectively). The annual HtTKV growth slope was significantly different across the evaluated time points in patients with an eGFR of 30–59 mL/min/1.73 m^2 (P=0.02). Additionally, the annual HtTKV growth slope was significantly lower at 12 months than at baseline (P=0.008). Similar results were observed for TKV and HtTKV.

Table 4 shows the comparison of secondary endpoints among groups categorized by final daily tolvaptan dose. Serum Cr levels were significantly lower at 12 months compared to baseline in the high dose group (P=0.04). Serum UA levels were significantly lower in the medium dose group (P=0.04). Serum Na^+ levels showed no significant differences across all dose groups. The annual HtTKV growth slope was significantly lower at 12 months than at baseline in the medium dose group (P=0.03), although the difference across the evaluated time points was not statistically significant. Similar results were observed for TKV and HtTKV.

Association of daily tolvaptan doses with sex, body weight, and body mass index

The average daily dose was 30 mg in male patients and

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Table 2 Changes in eGFR over the study duration for the overall population and patients categorized according to baseline eGFR and final daily tolvaptan dose

Group	0-month	1-month	2-month	4-month	8-month	12-month	Repeated measures ANOVA			Paired *t*-test	
							F	P value	Effect size	Difference (95% CI)	P value
Overall (n=43)	48.15±37.05	49.90±36.77	50.15±37.02	50.90±37.62	51.26±38.31	53.64±39.29	5.332	<0.001	0.002	5.48 (2.68–8.29)	<0.001
According to baseline eGFR (mL/min/1.73 m^2)											
≥90 (n=7)	114.13±14.83	111.69±16.15	111.89±16.95	114.33±12.94	112.19±20.84	117.32±13.59	0.782	0.57	0.017	3.20 (0.58–5.81)	0.02
60–89 (n=8)	67.91±7.51	70.57±14.59	70.02±13.51	71.05±13.98	74.36±19.72	77.60±15.68	2.173	0.08	0.051	9.69 (0.30–19.08)	0.045
30–59 (n=13)	43.31±8.31	48.01±9.17	48.99±12.62	49.00±13.32	49.52±12.52	52.47±12.45	4.128	0.03	0.057	9.16 (3.02–15.29)	0.007
15–29 (n=5)	17.95±4.94	18.14±5.66	17.58±4.79	17.85±6.46	17.45±5.47	17.47±6.76	0.128	0.98	0.003	–0.48 (–6.16 to 5.20)	0.82
0–14 (n=10)	7.56±2.97	8.45±4.41	8.81±5.84	9.39±8.20	9.29±8.77	9.48±10.14	0.533	0.49	0.010	1.93 (–3.79 to 7.64)	0.47
According to the final daily tolvaptan dose (mg)											
15 (n=14)	33.48±41.45	33.38±42.46	33.70±40.82	33.11±39.42	33.81±41.27	35.38±42.50	0.533	0.60	0.000	1.89 (–3.07 to 6.85)	0.42
>15–30 (n=22)	55.73±37.40	56.77±35.49	56.21±37.02	58.18±38.34	58.46±38.87	60.54±39.23	2.562	0.06	0.002	4.81 (1.99–7.63)	0.002
>30–60 (n=7)	53.68±15.62	61.33±13.65	63.97±14.02	63.63±16.45	63.51±14.90	68.45±17.28	4.655	0.04	0.089	14.77 (3.56, 25.99)	0.02

Data are presented as mean ± standard deviation. eGFR, estimated glomerular filtration rate; CI, confidence interval; ANOVA, analysis of variance.

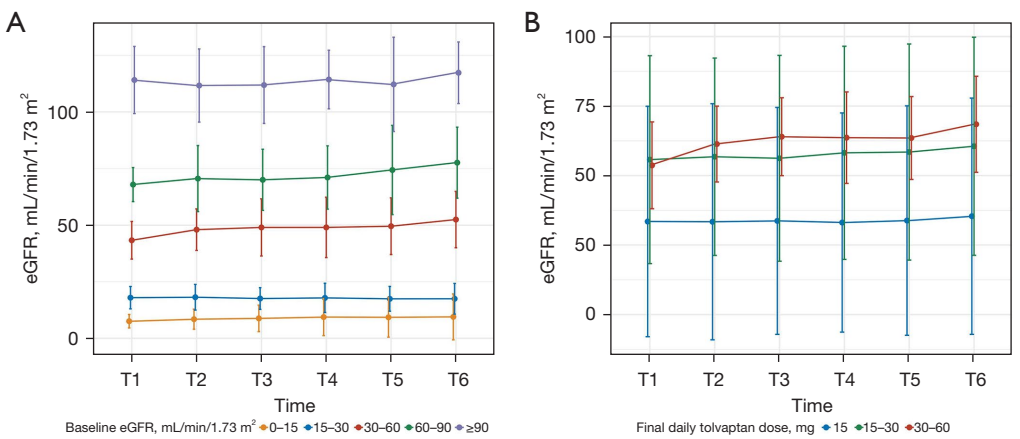

Figure 1 Changes in eGFR over the study duration in patients categorized according to baseline eGFR (A) and final daily tolvaptan dose (B). T1/T2/T3/T4/T5 and T6 mean: 0-, 1-, 2-, 4-, 8-, and 12-month, respectively. eGFR, estimated glomerular filtration rate.

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Table 3 Changes in secondary endpoints over the study duration for the overall population and patients categorized according to baseline eGFR

Time	Overall (n=43)	eGFR (mL/min/1.73 m^2)				
		≥90 (n=7)	60–89 (n=8)	30–59 (n=13)	15–29 (n=5)	0–14 (n=10)
Serum Cr levels (μmol/L)						
0-month	260.02±252.78	66.40±8.79	102.24±18.16	150.02±35.71	304.34±105.31	642.60±242.42
1-month	248.90±243.57	68.83±9.14	102.54±18.39	137.76±37.19	298.00±96.32	611.96±246.32
2-month	252.70±250.84	67.43±11.31	102.41±16.09	139.59±44.15	304.92±94.83	623.54±259.20
4-month	256.27±258.22	65.21±5.64	100.95±13.06	139.22±41.29	321.72±124.20	633.71±267.55
8-month	258.48±262.76	67.03±8.90	98.11±19.66	138.40±45.86	313.58±105.30	649.33±265.50
12-month	260.31±278.12	62.70±5.08	93.89±13.70	130.47±38.88	325.06±138.50	668.20±289.39
Repeated measures ANOVA						
F	0.762	0.836	1.174	3.743	0.954	0.900
P value	0.45	0.53	0.34	0.005	0.47	0.40
Effect size	0.000	0.058	0.039	0.021	0.009	0.005
Paired *t*-test						
Difference (95% CI)	0.29 (–20.50 to 21.09)	–3.70 (–7.65 to 0.25)	–8.35 (–20.27 to 3.57)	–19.56 (–28.85 to –10.26)	20.72 (–40.60 to 82.04)	25.60 (–70.76 to 121.96)
P value	0.98	0.06	0.14	<0.001	0.40	0.56
Serum UA levels (μmol/L)						
0-month	400.07±106.46	372.03±85.02	409.62±89.23	409.37±98.21	360.58±110.17	419.70±146.67
1-month	366.72±82.59	343.14±77.22	386.00±79.19	388.22±90.07	371.20±66.07	337.60±88.54
2-month	367.84±123.35	339.71±62.33	358.12±47.88	423.92±182.57	398.40±84.06	307.10±95.83
4-month	357.16±79.58	339.29±61.37	396.75±88.04	368.00±57.31	377.80±65.27	313.60±102.90
8-month	363.11±73.38	334.43±56.74	364.25±39.56	399.69±63.62	377.76±23.46	327.40±109.61
12-month	360.16±95.01	321.57±77.64	356.25±66.30	374.85±64.33	426.00±71.79	338.30±149.84
Repeated measures ANOVA						
F	2.282	1.370	1.459	1.142	0.613	2.242
P value	0.07	0.29	0.26	0.34	0.69	0.07
Effect size	0.023	0.051	0.085	0.037	0.093	0.099
Paired *t*-test						
Difference (95% CI)	–39.90 (–77.22 to –2.59)	–50.46 (–128.49 to 27.58)	–53.38 (–110.49 to 3.74)	–34.52 (–88.56 to 19.52)	65.42 (–113.44 to 244.28)	–81.40 (–209.31 to 46.51)
P value	0.04	0.16	0.06	0.19	0.37	0.18
Serum Na^+ levels (mmol/L)						
0-month	140.61±2.65	140.07±3.88	141.34±2.49	140.98±2.05	141.72±3.49	139.38±1.94
1-month	141.36±2.80	140.31±3.88	142.43±1.19	141.25±2.06	141.16±5.09	141.49±2.49
2-month	140.91±2.55	139.70±2.96	141.12±1.50	142.01±2.16	142.54±3.60	139.33±1.91
4-month	140.82±3.01	139.37±3.94	142.19±2.33	141.04±2.70	142.10±4.47	139.81±1.93
8-month	141.30±2.61	140.10±2.92	141.31±1.65	142.60±2.28	142.30±3.23	139.95±2.53
12-month	141.17±2.94	140.06±4.28	142.44±1.71	141.81±2.68	142.10±4.08	139.63±1.67

Table 3 *(continued)*

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Table 3 *(continued)*

Time	Overall (n=43)	eGFR (mL/min/1.73 m^2)				
		≥90 (n=7)	60–89 (n=8)	30–59 (n=13)	15–29 (n=5)	0–14 (n=10)
Repeated measures ANOVA						
F	2.148	0.392	2.545	5.157	0.537	3.019
P value	0.07	0.85	0.09	0.005	0.75	0.02
Effect size	0.010	0.008	0.092	0.063	0.015	0.118
Paired *t*-test						
Difference (95% CI)	0.56 (–0.02 to 1.13)	–0.01 (–2.11 to 2.08)	1.10 (–0.35 to 2.55)	0.83 (–0.25 to 1.91)	0.38 (–1.76 to 2.52)	0.25 (–1.18 to 1.68)
P value	0.056	0.99	0.12	0.12	0.65	0.70
HtTKV growth slope (%/year)						
0-month	4.91±2.04	4.39±2.95	4.36±1.62	4.56±2.00	5.17±0.76	6.03±1.99
4-month	4.82±2.08	4.17±3.15	4.47±1.79	4.37±1.89	5.09±0.84	6.25±1.70
8-month	4.73±2.09	4.02±2.91	4.57±1.79	4.15±2.04	4.93±0.77	5.99±1.93
12-month	4.74±2.04	4.24±2.74	4.47±1.56	4.04±1.97	5.07±1.19	6.03±1.94
Repeated measures ANOVA						
F	2.935	0.861	0.976	4.780	0.573	0.274
P value	0.050	0.48	0.42	0.02	0.64	0.69
Effect size	0.001	0.002	0.002	0.011	0.011	0.000
Paired *t*-test						
Difference (95% CI)	–0.17 (–0.33 to –0.01)	–0.15 (–0.69 to 0.39)	0.11 (–0.26, 0.48)	–0.51 (–0.86 to –0.16)	–0.10 (–0.82 to 0.63)	–0.00 (–0.14 to 0.13)
P value	0.04	0.51	0.51	0.008	0.73	0.94
TKV (mL)						
0-month	3,027.64±2417.62	959.03±474.96	1,953.23±1,178.16	2,524.10±1,095.15	3,814.23±2,106.44	5,596.50±3,174.65
4-month	2,931.98±2321.30	928.99±513.97	2,071.76±1,272.58	2,289.01±1,000.44	3,676.21±2,134.49	5,971.94±2,942.23
8-month	2,883.61±2407.08	892.41±509.32	2,168.32±1,347.20	2,134.11±1,116.02	3,473.13±2,210.62	5,529.28±3,049.80
12-month	2,947.72±2699.91	950.56±502.23	1,984.19±891.13	2,023.88±1,007.48	4,264.11±4,060.48	5,667.19±3,196.84
Repeated measures ANOVA						
F	0.727	0.919	0.933	4.862	0.541	0.353
P value	0.47	0.45	0.39	0.02	0.51	0.62
Effect size	0.000	0.003	0.006	0.033	0.014	0.001
Paired *t*-test						
Difference (95% CI)	–79.92 (–355.78 to 195.95)	–8.48 (–129.76 to 112.81)	30.96 (–366.10 to 428.03)	–500.22 (–837.15 to –163.29)	449.88 (–2,161.55 to 3,061.32)	62.86 (–549.86 to 675.58)
P value	0.562	0.870	0.859	0.007	0.66	0.82

Table 3 *(continued)*

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Table 3 *(continued)*

Time	Overall (n=43)	eGFR (mL/min/1.73 m^2)				
		≥90 (n=7)	60–89 (n=8)	30–59 (n=13)	15–29 (n=5)	0–14 (n=10)
HtTKV (mL/m)						
0-month	1,768.36±1,373.48	556.38±259.27	1,118.48±642.13	1,488.15±638.68	2,233.37±1,148.98	3,268.43±1,748.04
4-month	1,712.89±1,320.21	535.72±281.29	1,186.22±693.47	1,353.29±593.10	2,151.69±1,166.07	3,294.77±1,546.67
8-month	1,684.16±1,371.68	514.87±277.55	1,239.60±732.53	1,264.32±661.97	2,026.54±1,204.16	3,232.92±1,690.82
12-month	1,720.33±1,535.70	549.08±273.00	1,139.29±482.08	1,198.27±598.24	2,469.58±2,242.27	3,313.68±1,781.39
Repeated measures ANOVA						
F	0.758	0.938	0.928	5.029	0.522	0.339
P value	0.45	0.44	0.39	0.02	0.52	0.63
Effect size	0.000	0.004	0.006	0.032	0.014	0.001
Paired *t*-test						
Difference (95% CI)	–48.04 (–206.10 to 110.02)	–7.30 (–78.26 to 63.66)	20.81 (–201.84 to 243.46)	–289.89 (–481.31 to –98.46)	236.21 (–1,244.56 to 1,716.97)	40.65 (–325.78 to 407.09)
P value	0.54	0.81	0.83	0.006	0.68	0.81

Data are presented as mean ± standard deviation. UA, uric acid; eGFR, estimated glomerular filtration rate; Cr, creatinine; TKV, total kidney volume; HtTKV, height-adjusted total kidney volume; CI, confidence interval; ANOVA, analysis of variance.

Table 4 Changes in secondary endpoints over the study duration in patients categorized according to the final daily tolvaptan dose

Time	Final daily tolvaptan dose (mg)		
	15 (n=14)	>15–30 (n=22)	>30–60 (n=7)
Serum Cr levels (μmol/L)			
0-month	449.67±345.20	183.28±131.22	121.89±32.43
1-month	429.81±331.67	178.76±129.44	107.50±23.65
2-month	433.89±340.05	184.15±141.61	105.77±26.65
4-month	448.87±349.29	180.80±139.81	108.26±31.38
8-month	448.60±347.82	185.60±160.27	107.27±27.90
12-month	461.46±373.09	182.88±163.27	101.37±27.01
Repeated measures ANOVA			
F	0.715	0.230	3.452
P value	0.47	0.76	0.08
Effect size	0.001	0.000	0.055
Paired *t*-test			
Difference (95% CI)	11.78 (–46.00 to 69.57)	–0.40 (–22.92 to 22.13)	–20.51 (–39.12 to –1.91)
P value	0.67	0.97	0.04

Table 4 *(continued)*

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Table 4 *(continued)*

Time	Final daily tolvaptan dose (mg)		
	15 (n=14)	>15–30 (n=22)	>30–60 (n=7)
Serum UA levels (μmol/L)			
0-month	405.71±130.77	403.90±93.36	376.71±104.97
1-month	346.71±92.15	384.08±74.29	352.14±88.00
2-month	353.07±95.81	391.68±144.63	322.43±91.65
4-month	345.21±85.95	369.55±82.09	342.14±59.89
8-month	371.07±76.85	365.54±75.03	339.57±66.13
12-month	378.43±129.25	355.14±74.60	339.43±78.33
Repeated measures ANOVA			
F	1.424	1.479	0.926
P value	0.26	0.20	0.48
Effect size	0.043	0.031	0.044
Paired *t*-test			
Difference (95% CI)	−27.29 (−123.39 to 68.81)	−48.77 (−96.09 to −1.44)	−37.29 (−81.99 to 7.42)
P value	0.55	0.044	0.09
Serum Na^+ levels (mmol/L)			
0-month	140.26±2.95	140.58±2.30	141.44±3.30
1-month	141.69±3.61	140.80±2.28	142.48±2.33
2-month	140.16±3.22	140.94±2.05	142.31±2.20
4-month	140.24±3.39	140.57±2.85	142.75±2.16
8-month	140.34±3.21	141.56±2.01	142.43±2.75
12-month	140.05±3.31	141.41±2.73	142.64±2.24
Repeated measures ANOVA			
F	3.315	2.139	1.246
P value	0.01	0.08	0.32
Effect size	0.030	0.026	0.032
Paired *t*-test			
Difference (95% CI)	−0.21 (−0.97 to 0.56)	0.84 (−0.11 to 1.78)	1.20 (−0.19 to 2.59)
P value	0.57	0.08	0.08
HtTKV growth slope (%/year)			
0-month	5.68±2.28	4.50±1.92	4.63±1.74
4-month	5.87±2.08	4.31±2.02	4.69±1.72
8-month	5.61±2.12	4.23±2.04	4.51±1.90
12-month	5.72±2.12	4.24±1.96	4.33±1.57

Table 4 *(continued)*

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Table 4 *(continued)*

Time	Final daily tolvaptan dose (mg)		
	15 (n=14)	>15–30 (n=22)	>30–60 (n=7)
Repeated measures ANOVA			
F	0.596	2.673	1.497
P value	0.52	0.08	0.25
Effect size	0.000	0.003	0.007
Paired *t*-test			
Difference (95% CI)	0.04 (–0.22 to 0.30)	–0.26 (–0.49 to –0.03)	–0.31 (–0.89 to 0.27)
P value	0.73	0.03	0.24
TKV (mL)			
0-month	4,712.58±3,339.50	2,174.50±1,176.79	2,339.07±1,434.47
4-month	4,983.69±3,260.02	2,032.74±1,124.97	2,348.97±1,401.68
8-month	4,681.94±3,247.10	1,950.19±1,089.39	2,220.57±1,518.71
12-month	5,065.85±3,767.54	1,915.81±1,021.31	1,965.81±1,066.56
Repeated measures ANOVA			
F	1.283	3.160	1.831
P value	0.28	0.059	0.18
Effect size	0.003	0.008	0.015
Paired *t*-test			
Difference (95% CI)	347.68 (–411.14 to 1,106.50)	–258.69 (–487.59 to –29.79)	–373.26 (–884.07 to 137.54)
P value	0.34	0.03	0.12
HtTKV (mL/m)			
0-month	2,760.27±1,861.48	1,260.14±684.23	1,381.81±801.09
4-month	2,780.49±1,732.21	1,177.39±656.13	1,387.03±770.41
8-month	2,744.57±1,818.96	1,127.47±626.87	1,312.93±840.00
12-month	2,961.15±2,107.02	1,108.15±588.88	1,169.25±599.92
Repeated measures ANOVA			
F	1.260	3.329	1.835
P value	0.29	0.051	0.18
Effect size	0.003	0.009	0.015
Paired *t*-test			
Difference (95% CI)	197.59 (–236.81 to 631.99)	–152.00 (–283.30 to –20.69)	–212.57 (–506.66 to 81.52)
P value	0.34	0.02	0.13

Data are presented as mean ± standard deviation. UA, uric acid; Cr, creatinine; TKV, total kidney volume; HtTKV, height-adjusted total kidney volume; CI, confidence interval; ANOVA, analysis of variance.

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22.5 mg in female patients, with no significant difference between the 2 groups. The final daily dose was not correlated with body weight (r=–0.019, P=0.90) or body mass index (BMI; r=–0.014, P=0.93).

Cyst rupture and renal protection

During the study period, cyst rupture occurred in only 2 patients. Some 50% (n=5) of the patients with an eGFR of 0–14 mL/min/1.73 m^2 successfully delayed dialysis. The minimum duration of dialysis delay was 7 months in 2 patients, whereas the maximum duration of dialysis delay was 20 months in 1 patient.

Incidence of AEs

The only AE was mild thirst, with an incidence of 51.2%. In all affected patients, thirst was successfully relieved with patient education, diet adjustment, consumption of condiments with less salt, and sufficient water intake, with no impact on quality of life and work. No liver-associated AEs occurred in any of the patients, suggesting that lower-dose regimens were safe and well-tolerated.

Discussion

In this first clinical study of tolvaptan in Chinese patients with ADPKD, we evaluated the clinical effectiveness and optimal dose of tolvaptan during dose escalation over a period of 1 year. We found that the use of a lower tolvaptan dose could control the progression of the disease and that the AE of mild thirst could be gradually adjusted to significantly improve compliance by slowly increasing the dose. In the present study, 14 patients received a final daily tolvaptan dose of 15 mg. We did not find significant deteriorations in eGFR, annual HtTKV growth slope, and other indicators over the study period of 12 months. In addition, among 22 patients who received a final daily tolvaptan dose of >15–30 mg, eGFR and serum Cr levels were significantly improved compared to baseline, and the annual HtTKV growth slope, HtTKV, and TKV exhibited improvements. No significant increase in serum Na^+ levels occurred in the overall study population. Treatment with lower tolvaptan doses was not associated with any liver-related AEs, and the only AE was thirst, which was mild in all affected patients. The lowest recommended daily dose of tolvaptan is 60 mg (45 mg/15 mg) according to international guidelines (28,31). The Chinese guidelines recommend that tolvaptan should be started at a daily regimen of 15 mg/15 mg for a total daily dose of 30 mg. The present study results suggest that the starting dose of tolvaptan should be reconsidered in Chinese patients with ADPKD.

In a meta-analysis of 3,575 patients from 13 clinical studies, Lu *et al.* found that tolvaptan significantly reduced the slope of eGFR decline in patients with stage 2–4 chronic kidney disease and reduced the slope of TKV increase in patients with stage 1–3 chronic kidney disease, in agreement with the current study findings (15). Few clinical studies have evaluated the efficacy of tolvaptan in patients with an eGFR of <30 mL/min/1.73 m^2, for whom tolvaptan is relatively contraindicated according to the Chinese expert consensus. These patients are prone to frequent cyst rupture and infection, gross hematuria, and pain in daily life, which seriously impact the quality of life and compliance with treatment for chronic kidney disease. In the present study, 15 patients with an eGFR of <30 mL/min/1.73 m^2 had overt swelling and pain in the waist and abdomen. The cysts could be palpable under the skin in severe cases, and 14 patients had gross hematuria. Treatment with lower tolvaptan doses, with an average daily dose of 21 mg, controlled the disease, and key indicators such as TKV and eGFR at the end of 1 year were not significantly different from the baseline. Only 2 patients experienced cyst rupture, indicating the effectiveness of lower tolvaptan doses in controlling disease progression in these patients. Furthermore, dialysis was delayed in 5 (50%) patients with an eGFR of <15 mL/min/1.73 m^2, with dialysis delay times ranging from 7 to 20 months in 2 and 1 patients, respectively. These results further support the ability of lower-dose tolvaptan treatment to delay ADPKD progression and to postpone subsequent treatments such as renal transplantation. The observed effectiveness of lower tolvaptan doses for the treatment of ADPKD has significant implications in clinical practice, including reduced treatment costs for patients and alleviation of concerns regarding AEs such as liver injury and hypernatremia. Therefore, we recommend the widespread use of tolvaptan for the treatment of ADPKD in China without delay.

In addition to the use of tolvaptan, the management of ADPKD encompasses other important considerations. The diagnosis of ADPKD is not always straightforward, necessitating a careful differential diagnosis from autosomal recessive polycystic kidney disease, renal cysts and diabetes syndrome, renal lymphangioma, and so on (33). The management of ADPKD is a comprehensive process that

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includes lifestyle modifications, dietary management, disease-modifying treatments, and the management of complications such as nephrolithiasis with percutaneous nephrolithotomy (34,35).

The present study has several limitations. The size of the study population was small. We conducted post-hoc power calculations for all patient groups (see Appendix 1). The current sample size demonstrates sufficient power in the overall population. However, insufficient power was noted in specific groups, particularly among patients with baseline eGFR levels of 0–14 or 15–29 mL/min/1.73 m^2, as well as those in the low-dose group (Table S1). Therefore, the insignificant results in these groups should be interpreted with caution. This might be due to the limited awareness of the patients and clinicians regarding the need and the regimens for ADPKD treatment in China; these factors might have led to the failure of most eligible patients for study enrollment to be referred to the study hospital for tolvaptan treatment. Second, the present study aimed to explore the effectiveness of lower tolvaptan doses for disease control rather than the tolvaptan dose necessary for disease improvement; therefore, we did not use randomization. Finally, the treatment duration was relatively short, and clinical studies with longer treatment periods are necessary to demonstrate the clinical effectiveness and safety of lower tolvaptan doses.

Conclusions

In the present study, tolvaptan was found to be well tolerated at low doses, with no liver-associated AEs observed. Significant improvements in eGFR and reduced HtTKV growth were noted in the overall population and across various baseline eGFR and final dose groups. These results demonstrate the safety and effectiveness of lower tolvaptan doses in Chinese patients with ADPKD. Therefore, lower-dose tolvaptan treatment may be a suitable option for the management of ADPKD patients in China, potentially enhancing patient compliance and increasing clinician enthusiasm due to the reduced costs.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-448/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-448/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of China-Japan Friendship Hospital (No. 2023-KY-329) and individual consent for this retrospective analysis was waived.

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