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Long-Term Benefits of Treatment with Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Tolvaptan is the first effective drug treatment for autosomal dominant polycystic kidney disease (ADPKD) patients, but few long-term observations of the effects of tolvaptan have been reported.

Methods: In this single center, retrospective cohort study, we investigated nine patients who participated in a phase 3 trial of tolvaptan for ADPKD patients at our hospital between 2008 and 2014. Six of the patients discontinued tolvaptan at the end of the clinical trial and were defined as the discontinuation group, and three continued to take it; these were defined as the continuation group. The observation period was 3 years before and after the end of the tolvaptan trial, and we compared the following data in each group: serum creatinine, estimated glomerular filtration rate (eGFR), total kidney volume, serum sodium concentration, and urine specific gravity.

Results: eGFR was significantly improved after the end of the trial in the continuation group (P = 0.0446), but there was no significant change in the regression line before and after the end of the trial in the discontinuation group. The increases in mean total kidney volume rates over the 3 years before and after the trial were 0.01%/year vs. 0.067%/year in the discontinuation group (P = 0.0247). On the other hand, serum sodium concentration and urine specific gravity showed no change during the observation period.

Conclusion: This study suggested that long-term administration of tolvaptan may improve renal function and inhibit total kidney volume growth. (J Nippon Med Sch 2022; 89: 287–294)

Key words: autosomal dominant polycystic kidney disease, tolvaptan, renal function, total kidney volume, long-term treatment

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited renal disease in Japan and the fourth most common cause of dialysis initiation in the world[1]. Prevalence was 137 per 100,000 population in Japan in 2017, and it is estimated that 1 in 730 to 1,470 Japanese have ADPKD[1,2]. Before tolvaptan was introduced in December 14, 2010, revolutionizing the treatment of ADPKD[3,4], there was no effective treatment, and ADPKD was typically managed with conservative measures such as antihypertensive therapy with angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), and dietary therapy to prevent the progression of renal dysfunction.

There are two possible mechanisms for the adenosine 3′, 5′-monophosphate (cAMP)-mediated cyst growth observed in patients with ADPKD[5]. One is the formation of a complex in the cilia of the tubules by polycystin 1 and polycystin 2 (PC1/PC2), with PC2 opening the channel and causing an influx of Ca into the cell[6]. The second is an increase in cAMP concentration mediated by vasopressin V2 receptors, which are located on the basement membrane of tubular cells and are involved in urine concentration. In ADPKD, urine concentration is impaired

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and vasopressin concentration is high in the steady state[7], and it is thought that vasopressin increases cAMP via V2 receptors and G proteins, promoting renal cyst formation. Tolvaptan, a selective V2 receptor antagonist, is thought to suppress the production of cAMP, thereby inhibiting the growth of renal cysts.

Tolvaptan was shown in the global TEMPO 3:4 study[3] (reported in 2012) and subsequent phase 3 REPRISE study[8] (reported in 2017) to inhibit the progression of renal dysfunction and cyst enlargement, establishing its position as a standard treatment for ADPKD. However, few long-term clinical observations of patients with ADPKD have been reported. At our hospital, we conducted a domestic phase 3 clinical trial of tolvaptan from 2008 to 2014, and we were able to observe the drug's effects on patients with ADPKD for an even long period, because some of them wanted to continue taking it at their own expense after the trial ended. In this study, we investigated the long-term efficacy of tolvaptan by comparing the patients who continued treatment after the end of the trial with those who stopped.

Methods

Participants and Study Design

In this single center, retrospective cohort study, we investigated nine patients (four men, five women) with ADPKD who participated in a phase 3 trial of tolvaptan at our hospital between 2008 and 2014. Three of the patients continued to take tolvaptan at their own expense after the end of the clinical trial, and these were defined as the continuation group; the six patients who discontinued tolvaptan were defined as the discontinuation group. The observation period was from three years before the end of the tolvaptan trial to three years after, for a total of six years. Observations of individual patients were terminated if they had to undergo dialysis.

The following parameters were evaluated in each group: (1) estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2), (2) serum creatinine level (mg/dL), (3) total renal volume, (4) serum sodium concentration (mEq/L), and (5) urine specific gravity. The test results compiled during the observation period were collected retrospectively from the medical records. Blood and urine tests were performed every month, and the rotating ellipsoid volume calculation method[9,10] was used to calculate annual renal volume from MRI images, with the following formula used to estimate kidney volume: $\pi/6 \times$ renal long axis $\times$ maximum width orthogonal to the renal long axis[2].

Statistical Analysis

All laboratory values are presented as means ± standard deviation. Continuous variables were compared with the unpaired t-test, and Fisher's exact test was used for various inter-group comparisons. One-way analysis of variance (ANOVA) was performed on the longitudinal data to address its multiplicity. Tukey's multiple comparison test was used as the post-hoc test. P values < 0.05 were considered statistically significant for all analyses performed. Regression lines were separately determined for the respective data. All statistical analyses were performed with Prism® software version 8 (GraphPad Software, La Jolla, CA, USA).

Statement of ethics: The study protocol was approved by the Ethics Committee of Nippon Medical School Hospital (27-07-465) and designed in accordance with the Declaration of Helsinki. The study was registered with the University Hospital Medical Information Network (UMIN No. 000033968).

Consent: All participants signed written informed consent forms, which included information about the research. Confidentiality of information and anonymity were also preserved in this study.

Results

Baseline Characteristics of Participants

Table 1 shows the baseline characteristics of the nine patients at the end of the phase 3 trial. There were no significant differences between the two groups in BMI, blood pressure, complications, medications used, renal function, urine specific gravity, or total renal volume. In each group, there was one patient who underwent dialysis during the observation period (**Table 1**).

Renal Function

Figure 1, 2 show the changes in serum creatinine and eGFR during the observation period in each group. The regression lines of serum creatinine levels before and after the end of the study were $Y = 0.006480*X + 1.419$ (before) and $Y = -0.02272*X + 2.685$ (after) in the discontinuation group, and $Y = 0.01211*X + 0.9104$ and $Y = 0.002102*X + 1.543$ in the continuation group, with no significant differences between the pre- and post-trial values ($p = 0.2051$ and $p = 0.4581$, respectively) (**Fig. 3**). On the other hand, while the regression lines of eGFR showed no significant change in the discontinuation group before and after the end of the study ($Y = -0.0261*X + 46.53$, $Y = 0.01183*X + 37.31$, $p = 0.8794$), they showed significant change in the continuation group ($Y = -0.3577*X + 61.64$, $Y = 0.1561*X + 44.70$, $p = 0.0446$)

Table 1 Baseline characteristics of patients at the end of the phase 3 trial

total, n	Discontinuation group n = 6	Continuation group n = 3	*P* Value
Women, n (%)	4 (66.7)	1 (33.3)	0.524
Age (years)	46.5 ± 8.09	61.99 ± 15.25	0.925
BMI (kg/m^2)	24.92 ± 3.69	21.53 ± 1.86	0.188
Diabetes mellitus, n (%)	0 (0)	0 (0)	
Hypertension, n (%)	4 (66.7)	2 (66.7)	>0.9999
Valvular heart disease, n (%)	0 (0)	0 (0)	
Cerebral aneurysm, n (%)	0 (0)	0 (0)	
CVD, n (%)	1 (16.7)	0 (0)	>0.9999
RASi, n (%)	4 (66.7)	2 (66.7)	>0.9999
Systolic BP (mmHg)	140.2 ± 19.3	125.7 ± 6.4	0.257
Diastolic BP (mmHg)	85.2 ± 11.1	82.3 ± 1.5	0.683
Heart rate (bpm)	69.8 ± 6.3	66.0 ± 16.8	0.621
AST (U/L)	20.7 ± 4.4	20.3 ± 9.5	0.942
ALT (U/L)	18.7 ± 6.6	16.7 ± 7.5	0.694
UA (mg/dL)	5.95 ± 1.91	6.00 ± 0.09	0.966
BUN (mg/dL)	19.6 ± 12.3	19.6 ± 6.2	0.998
Cre (mg/dL)	1.54 ± 1.19	1.32 ± 0.61	0.775
Alb (g/dL)	4.21 ± 0.24	4.23 ± 0.37	0.938
Na (mEq/L)	139.5 ± 1.4	139.0 ± 1.7	0.649
Cl (mEq/L)	107.5 ± 2.1	105.6 ± 4.2	0.391
K (mEq/L)	4.10 ± 0.38	4.40 ± 0.30	0.285
Ca (mg/dL)	8.60 ± 0.40	8.95 ± 0.07	0.297
P (mg/dL)	3.36 ± 0.63	3.80 ± 0.14	0.397
eGFR (mL/ min/1.73 m^2)	48.2 ± 23.2	48.0 ± 16.5	0.992
CRP (mg/dL)	0.056 ± 0.025	0.077 ± 0.083	0.556
Urine specific gravity	1.0077 ± 0.0048	1.0067 ± 0.0007	0.809
WBC (/μL)	5,366.7 ± 1,093.1	5,066.7 ± 763.7	0.687
Hb (g/dL)	12.56 ± 1.70	13.13 ± 1.65	0.650
Plt (*10^4/μL)	18.75 ± 7.59	25.30 ± 6.72	0.248
Kidney volume (cm^3)	1,834.4 ± 831.5	1,465.8 ± 655.6	0.528
ESRD	1 (16.7)	1 (33.3)	>0.9999

BMI: body mass index, CVD: cardiovascular disease, RASi: renin-angiotensin-aldosterone system inhibitor, BP: blood pressure, AST: aspartate aminotransferase, ALT: alanine aminotransferase, UA: uric acid, BUN: blood urea nitrogen, Cre: creatinine, Alb: albumin, Na: sodium, K: potassium, Ca: calcium, P: phosphorus, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, WBC: white blood cell, Hb: hemoglobin, Plt: platelet, ESRD: end stage renal disease

(**Fig. 4**), indicating improvement in eGFR.

Total Kidney Volume

Neither group showed significant change in total kidney volume over the study period (discontinuation group: from 1,663.7 +/− 626.5 (cm^3) to 2,112.9 +/− 322.2 (cm^3), ANOVA: p = 0.0536; continuation group: from 1,332.3 +/− 620.2 (cm^3) to 1,430.1 +/− 896.8 (cm^3), ANOVA: p = 0.3304). However, a significant difference was observed in the discontinuation group when Tukey's multiple comparison test was used as a post-hoc test (−3 vs. 3, p = 0.0247) (**Fig. 5**).

Serum Sodium Concentration, Urine Specific Gravity

ANOVA was used to assess serum sodium concentration and urine specific gravity three times in each group: at the beginning of the observation, at the end of the trial, and at the end of the observation. Serum sodium concentration showed a tendency to decrease in the discontinuation group, but without statistical significance (p = 0.0536), and a tendency to increase in the continuation group, but also without statistical significance (p = 0.3304) (**Fig. 6**). Nor was any significant change in urine specific gravity observed in either group (p = 0.5532 in the discontinuation group, p = 0.7837 in the continuation group) (**Fig. 7**).

Adverse Reactions

Although hepatic dysfunction has been cited as an im-

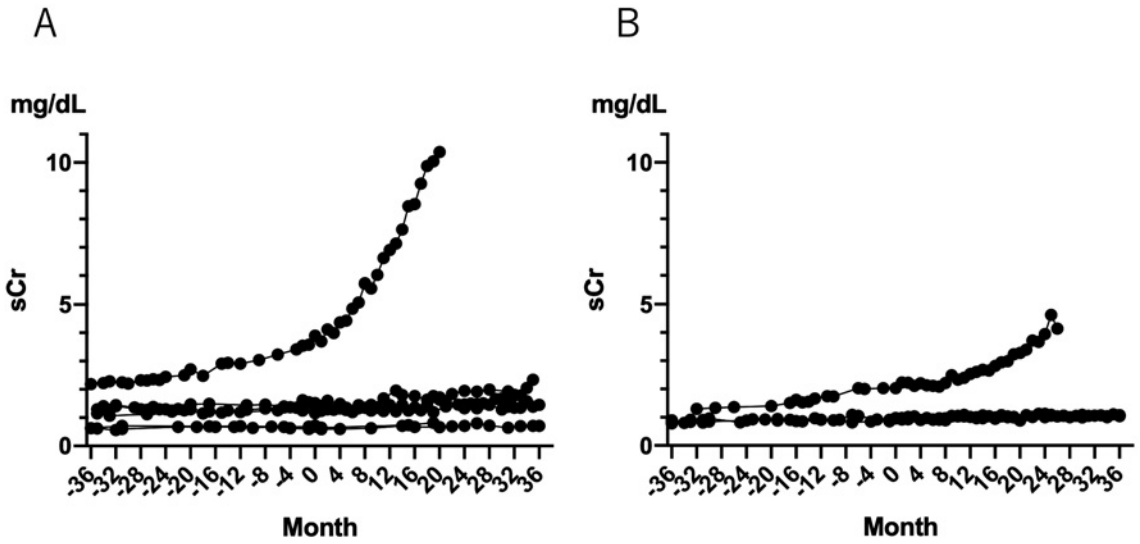

Fig. 1 Changes in serum creatinine during the observation period
A: discontinuation group, B: Continuation group

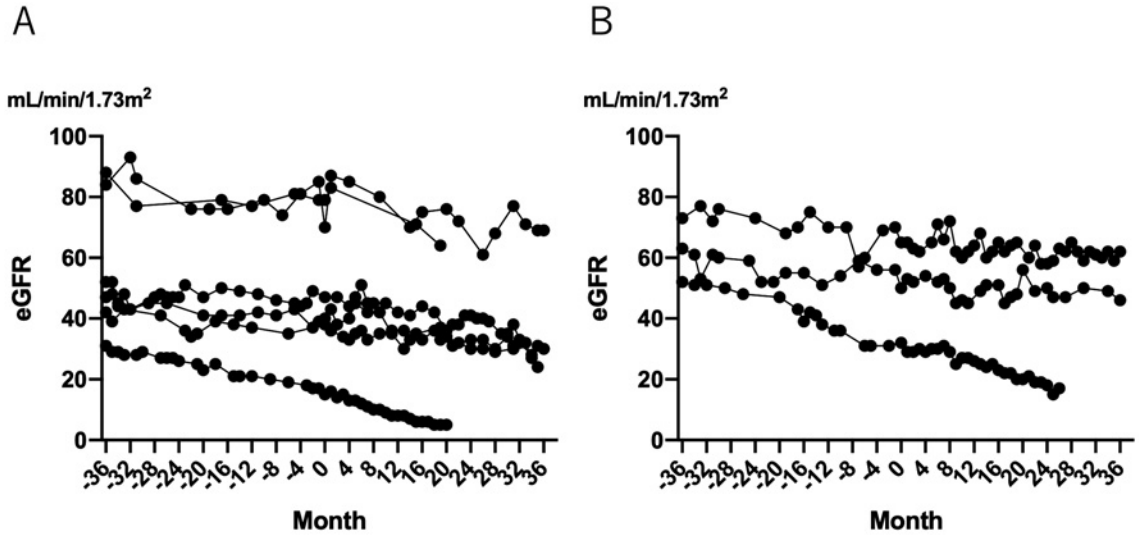

Fig. 2 Changes in eGFR during the observation period
A: discontinuation group, B: Continuation group
eGFR: estimated glomerular filtration rate

portant adverse effect of tolvaptan, we encountered no cases that led to dose reduction or discontinuation of the drug during the observation period. Nor were there any cases of discontinuation due to other side effects.

Discussion

Renal Function

Tolvaptan was originally used to treat fluid retention in heart failure, and its effects on renal function have been demonstrated in the acute[11] and chronic[12] phases, as well as after peritoneal dialysis introduction[13]. Its effects are particularly pronounced in chronic kidney disease (CKD) complicated by chronic heart failure[14].

The TEMPO 3:4 study, the largest clinical study of its kind, showed that tolvaptan inhibited the decline of renal function in patients with ADPKD, and that it improved serum creatinine levels from the first year of treatment: the difference in serum creatinine levels between the tolvaptan and placebo groups was 2.02 mg/mL ($p < 0.001$) at the end of the first year of observation, and 3.68 mg/mL ($p < 0.001$) at the end of the third year, demonstrating that the effect continued into the third year. The annual rate of change in eGFR was reported to be -2.72 mL/min/1.73 m^2 in the tolvaptan group, and

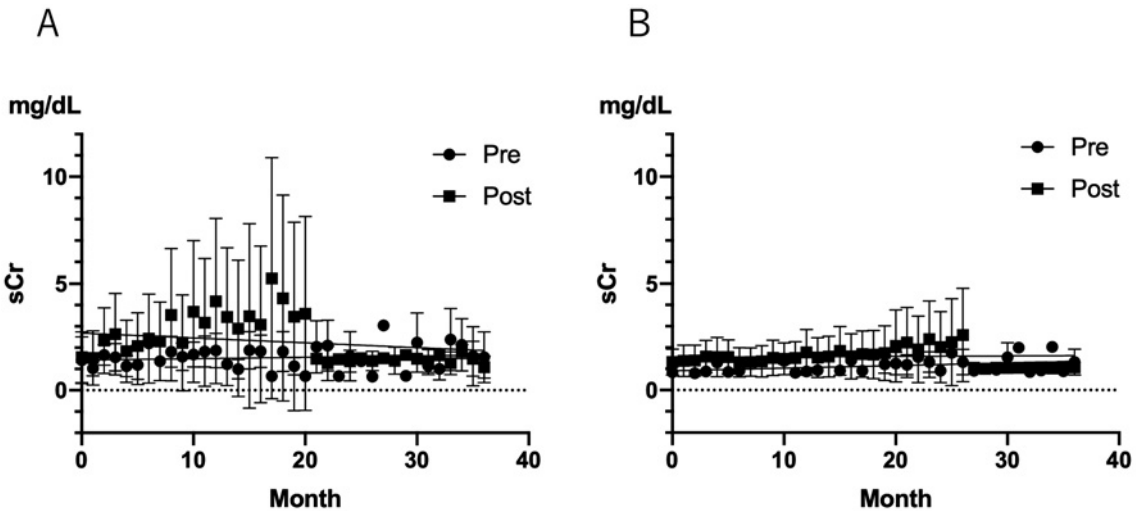

Fig. 3 Comparison of gradients of the regression lines of serum creatinine levels before and after the end of the phase 3 trial
A (discontinuation group): Y = 0.006480*X + 1.419 (before), Y = –0.02272*X + 2.685 (after) (p = 0.2051)
B (continuation group): Y = 0.01211*X + 0.9104 (before), Y = 0.002102*X + 1.543 (after) (p = 0.4581)

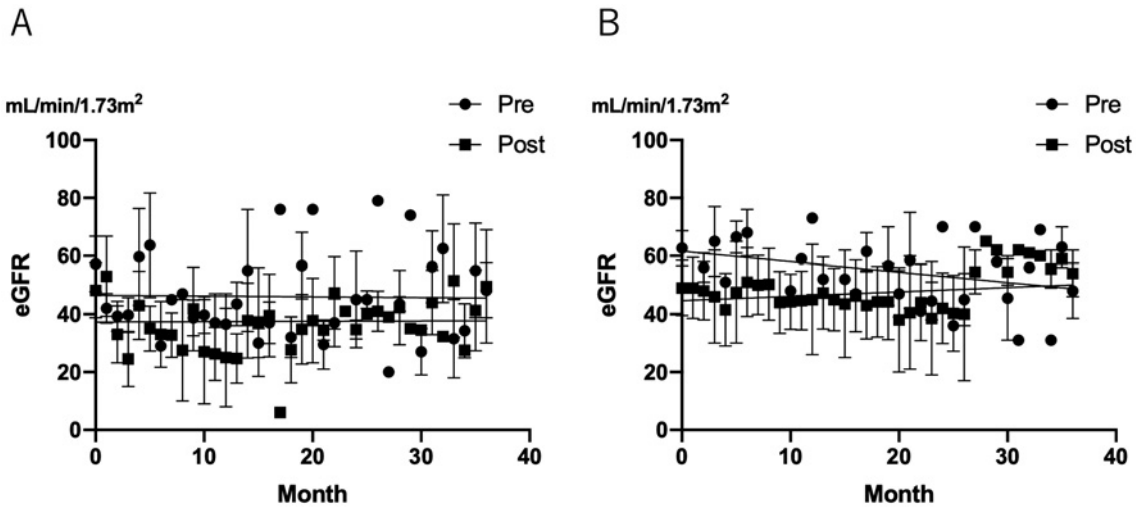

Fig. 4 Comparison of gradients of the regression lines of eGFR levels before and after the end of the phase 3 trial
A (discontinuation group): Y = –0.0261*X + 46.53 (before), Y = 0.01183*X + 37.31 (after) (p = 0.8794)
B (continuation group): Y = –0.3577*X + 61.64 (before), Y = 0.1561*X + 44.70 (after) (p = 0.0446)
eGFR: estimated glomerular filtration rate

−3.70 mL/min/1.73 m^2 in the placebo group.

In our study, we compared results between patients who continued taking tolvaptan after the end of our Phase 3 clinical trial of the drug and those who did not. In the discontinuation group, there was no worsening of renal function due to discontinuation, but in the continuation group, there was an improvement in the rate of decline of eGFR in the latter half of the observation period (p = 0.0446). This could be considered as an effect of long-term medication, although it is inconsistent with the TEMPO 3:4 study. On the other hand, there was no significant difference in serum creatinine levels, but this may be due to the large confounding effect of age due to the small number of patients.

Although long-term observational studies have been carried out to compare tolvaptan and placebo groups[15], this is the first to investigate patients after they discontinued medication.

Total Kidney Volume

A previous study showed that the annual increase in renal volume was significantly reduced in patients taking tolvaptan (2.8% in the tolvaptan group vs. 5.5% in the

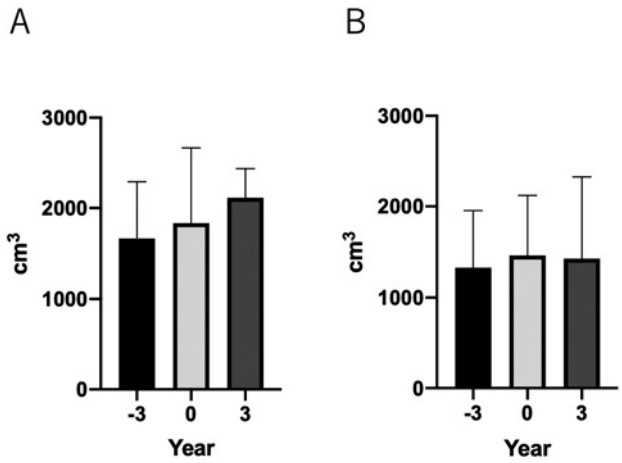

Fig. 5 Overall changes in total kidney volume
A (discontinuation group): Significant according to the results of one-way ANOVA (p = 0.0536) and Tukey's multiple comparison testing (–3 vs. 3, p = 0.0247)
B (continuation group): Not significant according to the results of one-way ANOVA (p = 0.3304)

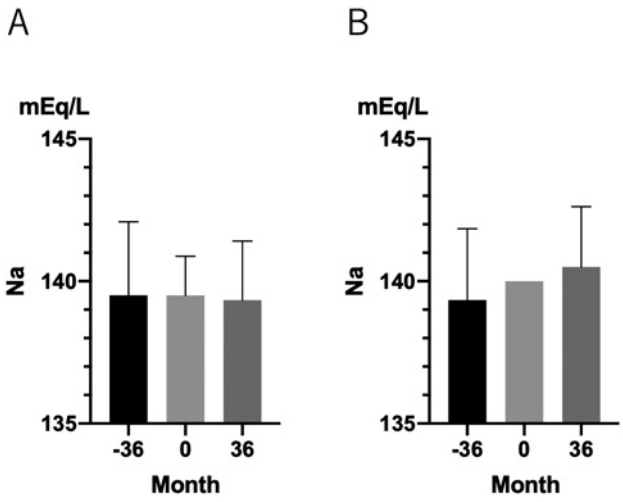

Fig. 6 Overall changes in serum sodium concentration
A (discontinuation group): Not significant according to the results of one-way ANOVA (p = 0.0536)
B (continuation group): Not significant according to the results of one-way ANOVA (p = 0.3304)

placebo group) after 3 years of follow-up (TEMPO 3:4 study)[3]. Another showed that the effect of tolvaptan on cyst growth was strongest in the first year of medication with tolvaptan and diminished after the second year (TEMPO 4:4 study)[16]. In addition, tolvaptan has also been reported to inhibit cyst growth in patients with advanced CKD[17]. In our study, the mean rate of renal volume increase in the discontinuation group was 0.01%/year during the 3 years of tolvaptan therapy, and 0.067%/year in the 3 years after discontinuation. No obvious increase was observed in the continuation group, however, which

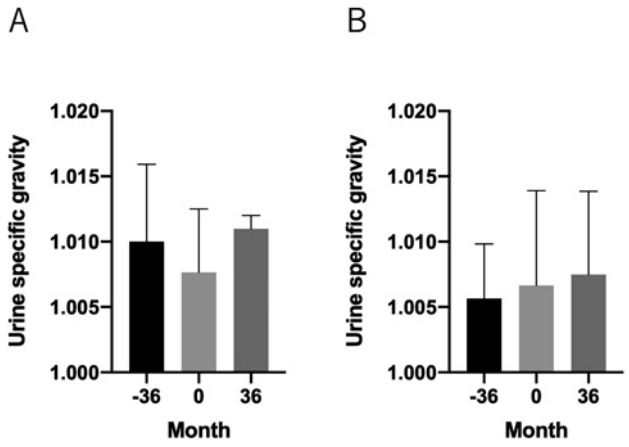

Fig. 7 Overall changes in urine specific gravity
A (discontinuation group): Not significant according to the results of one-way ANOVA (p = 0.5532)
B (continuation group): Not significant according to the results of one-way ANOVA (p = 0.7837)

could be attributed to the effect of continued administration of tolvaptan.

Serum Sodium Concentration, Urine Specific Gravity

Tolvaptan is a novel, orally active, selective non-peptide antagonist that inhibits arginine vasopressin from binding to V2 receptors in the distal nephron, inducing the excretion of electrolyte-free water without altering total electrolyte excretion[18]; it was approved for the treatment of hyponatremia in the US and Europe in 2009[19–21]. Its use in the treatment of ADPKD, however, may cause hypernatremia as a side effect: in the TEMPO 3:4 study, the tolvaptan group experienced elevated serum sodium levels of at least 2.5 mmol/L per year, with 4.0% of patients in the tolvaptan group and 1.0% of patients in the placebo group experiencing elevated levels of 150 mmol/L or more. In our study, serum sodium tended to increase with tolvaptan administration. Although we observed no significant difference in serum sodium levels after tolvaptan discontinuation (possibly because of the small number of patients in the study), there was a tendency for serum sodium to decrease and urine specific gravity to increase.

Limitations

Because this was a single center, retrospective cohort study, the number of participants was too small to allow robust statistical analysis, which may have led to various biases. Further large-scale, prospective studies are required to confirm our results.

Conclusion

Our study showed that total renal volume was signifi-

cantly increased after 3 years in patients who discontinued tolvaptan, while the rate of deterioration of renal function was significantly improved in those who continued taking the drug, suggesting that long-term administration of tolvaptan may preserve renal function.

Data Availability: All data generated or analyzed during this study are available from the corresponding author on request.

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Authors' Contributions: NS drafted the first manuscript. NS, MI, YT, SK, AH, TK and YS managed the patients. YT helped with writing the manuscript. YS coordinated the data analysis and helped with writing the manuscript. All authors participated in discussions, and read and approved the final manuscript.

Conflict of Interest: The authors have no conflicts of interest to declare.

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