ORIGINAL

Clinical characteristics associated with 1-year tolvaptan efficacy in autosomal dominant polycystic kidney disease with a wide range of kidney functions

Taichi Murakami[1)2)], Kenji Nishimura[2)], Hiroyuki Ono[2)], Sayo Ueta[2)], Eriko Shibata[2)], Seiji Kishi[2)], Masanori Tamaki[2)], Keiko Miya[3)], Hisato Shima[4)], Manabu Tashiro[4)], Tomoko Inoue[4)], Kazuhiko Kawahara[4)], Kojiro Nagai[2)], Hideharu Abe[2)], Jun Minakuchi[4)], and Toshio Doi[2)]

[1)]Department of Nephrology, Ehime Prefectural Central Hospital, Ehime, Japan, [2)]Department of Nephrology, Graduate School of Biomedical Science, Tokushima University, Tokushima, Japan, [3)]Department of Internal Medicine, Kawashima Hospital, Tokushima Japan, [4)]Department of Kidney Disease, Kawashima Hospital, Tokushima Japan

Abstract : Autosomal dominant polycystic kidney disease (ADPKD) develops into end-stage kidney disease by 65 years of age in an estimated 45%-70% of patients. Recent trials revealed that tolvaptan inhibits disease progression both in early-stage or late-stage ADPKD ; however, stratified analysis showed a difference of favorable factors correlated with tolvaptan efficacy between early-stage and late-stage ADPKD. Thus, we examined the efficacy of tolvaptan in ADPKD with a wide range of estimated glomerular filtration rates (eGFR). We enrolled 24 patients with eGFR 35.3 (28.0-65.5) ml/min/1.73m² and evaluated treatment effect as ΔΔeGFR (ml/min/1.73m²/year) or ΔΔtotal kidney volume (TKV) (%/year) that was calculated as post-treatment annual change - pre-treatment annual change. Pre ΔeGFR was significantly low in eGFR responders, defined as ΔΔeGFR > 0 ml/min/1.73m²/year. In eGFR responders, pre ΔeGFR, post ΔeGFR, eGFR, TKV, and proteinuria were significantly correlated with ΔΔeGFR. In TKV responders defined as ΔΔTKV > 5 %/year, we identified hypertension history, proteinuria, TKV, and post ΔTKV as significantly correlated factors with ΔΔTKV. In conclusion, pre ΔeGFR may be a predictive factor of therapeutic efficacy on kidney function. Tolvaptan may have greater efficacy in early-stage ADPKD with rapid GFR decline or with well-controlled blood pressure. J. Med. Invest. 67 : 315-320, August, 2020

Keywords **:** *autosomal dominant polycystic kidney disease, tolvaptan, theraputic efficacy*

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease caused by mutations in the genes encoding polycystin 1 (PKD1) or polycystin 2 (PKD2). Progression of the disease is inexorable with an estimated 45%-70% of patients developing end-stage kidney disease by the age of 65. Mutations in PKD1 or PKD2 elevate the levels of intracellular adenosine 3', 5'-cyclic monophosphate (cAMP) (1, 2). The high intracellular cAMP promotes fluid secretion and renal tubular cell proliferation (3), which results in cyst formation. Vasopressin promotes kidney-cyst cell proliferation and fluid secretion into cysts by means of upregulation of cAMP in renal tubular cells. Genetic elimination of circulating vasopressin or pharmacological V2 receptor blockade inhibits disease progression in animal models orthologous to human ADPKD (4-6).

Phase 3, randomized, double-blind, placebo-controlled trials have revealed that tolvaptan, vasopressin V2-receptor blocker, reduces cyst burden and protects kidney function compared with placebo both in patients with early-stage or late-stage ADPKD (7-9). Interestingly, stratified analysis in these studies showed that a difference of favorable factors correlated with tolvaptan efficacy on kidney function or volume between early-stage and late-stage ADPKD. TEMPO 3 : 4, a 3-year trial that examined patients with early-stage ADPKD with estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73m², clarified that tolvaptan was more effective in more advanced patients with age ≧ 35 years or total kidney volume (TKV) ≧ 1500 ml. In contrast, the REPRISE trial proved the efficacy and safety of tolvaptan in late-stage patients with eGFR 25 to 65 ml/min/1.73m², wherein tolvaptan was more effective in early-stage patients with age ≦ 55 years or with chronic kidney disease (CKD) stage 3a (eGFR 45 to 59 ml/min/1.73m²). In practical clinic settings, we often administer tolvaptan in patients with CKD stage 1-4 and observe that the response to tolvaptan varies clinically. Some patients present adverse effects of tolvaptan. Clarifying the determinant of the responsiveness to tolvaptan is clinically crucial to treat patients more efficiently. Therefore, we examined the clinical characteristics associated with tolvaptan efficacy on kidney function and kidney volume in patients with a wide range of GFR.

PATIENTS AND METHODS

Design and subjects

We administered tolvaptan to 34 patients with ADPKD in our hospitals between May 2015 and December 2017 and enrolled 24 patients who were followed for more than 1 year after tolvaptan administration in this study. During the follow-up period, we excluded four patients because of discontinuation of tolvaptan due to liver dysfunction and excluded one patient due to end-stage kidney disease. We also excluded patients whose annual eGFR change for more than 1 year before tolvaptan initiation was unknown or patients with eGFR > 90 ml/min/1.73m² at tolvaptan administration. eGFR was calculated from serum creatinine and age by using the 3-variable Japanese equation as follows : eGFR

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Address correspondence and reprint requests to Taichi Murakami, 83 Kasuga, Matsuyama, Ehime 790-0024 Japan and Fax : +81-89-943-4136.

(ml/min/1.73m²) = 194 × Age$^{-0.287}$ × Creatinine (mg/dL)$^{-1.094}$ (× 0.739 if female). TKV was calculated by the ellipsoid rotation method. Pre ΔeGFR (ml/min/1.73m²/year) and pre ΔTKV (%/year) were defined as the annual eGFR change and the annual TKV change before tolvaptan administration, respectively. Post ΔeGFR (ml/min/1.73m²/year) was defined as the annual eGFR change for 1 year after tolvaptan initiation. Patients with tolvaptan administration frequently show the initial drop of eGFR, therefore we started to follow post ΔeGFR one month after tolvaptan initiation. One year after tolvaptan initiation, we re-evaluated TKV, and post ΔTKV (%/year) was defined as the annual TKV change. ΔΔeGFR was calculated as follows : ΔΔeGFR (ml/min/1.73m²/year) = post ΔeGFR – pre ΔeGFR. ΔΔTKV was calculated as follows : ΔΔTKV (%/year) = post ΔTKV – pre ΔTKV. We evaluated the response to tolvaptan in ADPKD as ΔΔeGFR and ΔΔTKV. Unfortunately, we were not able to measure TKV 1 year after tolvaptan initiation in 1 patient, thus statistical analysis of ΔΔTKV was performed in total 23 patients. We evaluated TKV and eGFR at tolvaptan initiation and urine osmolality after tolvaptan initiation. We measured mean blood pressure and urine volume during hospitalization for tolvaptan administration. Tolvaptan dosage was adjusted in accordance with patient's consent and tolerability and corrected by body surface area.

Statistical analysis

The results are shown as mean ± standard deviation, as number (%) or as median (interquartile range) if skewed. A test for normality was performed using the Kolmogorov-Smirnov test. *P* value was calculated with student's *t*-test in parametric variables or Mann -Whitney's U test was used in non-parametric variables between two groups. A *p* value ≦ 0.05 was considered significant. Statistical analyses were performed with IBM SPSS statics.

Ethical approval

This study was approved by the Ethics Committee of Tokushima University Hospital (No.3105-2) and Kawashima Hospital (No.0395), and was performed in compliance with the Helsinki Declaration. We provided all individual patients with the option to opt out of participation.

Table 1. Baseline characteristics of enrolled participants

	N = 24
age (year)	52.2 ± 8.8
male, n (%)	17 (70.8)
family history of ADPKD, n (%)	18 (75.0)
hypertension, n (%)[a]	22 (91.7)
liver cyst, n (%)[a]	21 (87.5)
cerebral aneurysm, n (%)[a]	2 (8.3)
proteinuria, n (%)[a]	9 (37.5)
systolic BP (mmHg)[a]	128.5 ± 11.1
diastolic BP (mmHg)[a]	78.3 ± 9.9
eGFR (ml/min/1.73m^2)[a]	35.3 (28.0-65.5)
TKV (L)[a]	2.1 (1.4-2.9)
urine volume (L/day)[a]	5.8 ± 2.3
urine osmolality (mmH_2O)	113.0 ± 42.3
BSA-corrected tolvaptan dosage (mg/day/m^2)	34.3 (32.0-38.1)
pre ΔeGFR (ml/min/1.73m^2/year)	-4.8 ± 2.9
post ΔeGFR (ml/min/1.73m^2/year)	-1.8 ± 4.2
ΔΔeGFR (ml/min/1.73m^2/year)	3.0 ± 5.9
pre ΔTKV (%/year)	9.9 (5.8-14.7)
post ΔTKV (%/year)	-4.0 ± 13.1
ΔΔTKV (%/year)	-15.2 ± 15.5

Data are presented as mean ± standard deviation, as number (%) or as median (interquartile range) if skewed. [a]Data are shown at hospitalization for tolvaptan administration. ADPKD, Autosomal dominant polycystic kidney disease ; BP, blood pressure; eGFR, estimated glomerular filtration rate; TKV, total kidney volume; BSA, body surface area.

RESULTS

Baseline characteristics of enrolled patients

In this study, we enrolled 24 patients (male : 17 [70.8%], female : 7 [29.2%]) with ADPKD treated with tolvaptan in Tokushima University Hospital or Kawashima Hospital. Baseline characteristics are shown in Table 1. Their mean age was 52.2 ± 8.8 years. The median eGFR and TKV after tolvaptan administration were 35.3 (28.0-65.5) ml/min/1.73m² and 2.1 (1.4-2.9) L, respectively, thus indicating that patients with late-stage ADPKD were examined in this study. The mean post ΔeGFR was -1.8 ± 4.2 ml/min/1.73m²/year, which was significantly improved by tolvaptan ($p < 0.05$*, the mean pre ΔeGFR : -4.8 ± 2.9 ml/min/1.73m²/year). The mean post ΔTKV (-4.0 ± 13.1 %/year) was significantly decreased by tolvaptan ($p < 0.01$**, the median pre ΔTKV : 9.9 [5.8-14.7] %/year) (Figure 1). These data suggest tolvaptan is effective for preserving kidney function and for TKV reduction during 1 year.

Comparison between responders and non-responders in ΔΔeGFR or ΔΔTKV

Initially, we compared clinical characteristics between responders and non-responders (Table 2). We defined a responder as follows : ΔΔeGFR > 0 ml/min/1.73m²/year or ΔΔTKV

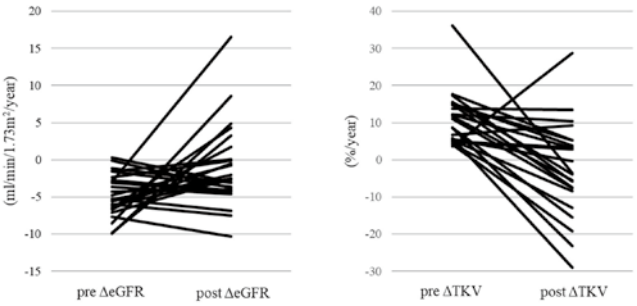

Figure 1. The effect of tolvaptan on ΔeGFR and ΔTKV
Pre ΔeGFR (ml/min/1.73m²/year) and pre ΔTKV (%/year) were defined as the annual eGFR change and the annual TKV change before tolvaptan administration, respectively. Post ΔeGFR (ml/min/1.73m²/year) and post ΔTKV (%/year) were defined as the annual eGFR and TKV change for 1 year after tolvaptan initiation, respectively. The mean post ΔeGFR was -1.8 ± 4.2 ml/min/1.73m²/year, which was significantly improved ($p < 0.05$*, the mean pre ΔeGFR : -4.8 ± 2.9 ml/min/1.73m²/year). The mean post ΔTKV (-4.0 ± 13.1 %/year) was significantly decreased ($p < 0.01$**, the median pre ΔTKV : 9.9 [5.8-14.7] %/year). eGFR, estimated glomerular filtration rate; TKV, total kidney volume.

Table 2. Comparison between responders and non-responders in ΔΔeGFR and ΔΔTKV

	ΔΔeGFR			ΔΔTKV[b]		
	responder	non-responder	*p* value	responder	non-responder	*p* value
	N = 14	N = 10		N = 15	N = 8	
age (year)	52.6 ± 9.6	51.7 ± 8.2	0.82	52.1 ± 7.0	55.0 ± 9.2	0.41
male, n (%)	10 (71.4)	7 (70.0)	0.81	9 (60.0)	7 (87.5)	0.18
family history of ADPKD, n (%)	10 (71.4)	8 (80.0)	0.64	12 (80.0)	5 (62.5)	0.37
hypertension, n (%)[a]	13 (92.8)	9 (90.0)	0.81	13 (86.7)	8 (100.0)	0.29
liver cyst, n (%)[a]	12 (85.7)	9 (90.0)	0.76	14 (93.3)	6 (75.0)	0.22
cerebral aneurysm, n (%)[a]	1 (7.1)	1 (10.0)	0.81	2 (13.3)	0 (0.0)	0.29
proteinuria, n (%)[a]	8 (57.1)	1 (10.0)	< 0.05*	6 (40.0)	3 (37.5)	0.91
systolic BP (mmHg)[a]	128.6 ± 8.4	128.5 ± 14.5	0.98	127.1 ± 5.8	131.1 ± 18.0	0.43
diastolic BP (mmHg)[a]	77.1 ± 10.6	80.0 ± 9.1	0.50	78.8 ± 8.8	76.0 ± 11.9	0.53
eGFR (ml/min/1.73m^2)[a]	41.0 ± 19.9	49.4 ± 20.4	0.33	44.0 (31.0-66.5)	30.5 (27.8-36.0)	0.20
TKV (L)[a]	2.6 ± 1.3	2.1 ± 1.2	0.35	2.4 ± 1.2	2.7 ± 1.6	0.52
urine volume (L/day)[a]	5.5 ± 2.3	6.2 ± 2.5	0.54	5.7 ± 1.9	5.9 ± 3.3	0.87
urine osmolality (mmH_2O)	118.0 ± 48.0	105.1 ± 36.3	0.50	112.8 ± 43.0	114.4 ± 49.6	0.68
BSA-corrected tolvaptan dosage (mg/day/m^2)	34.3 (31.7-38.3)	34.7 (32.5-36.1)	0.73	35.0 ± 7.0	37.0 ± 10.3	0.58
pre ΔeGFR (ml/min/1.73m^2/year)	-6.1 ± 2.4	-3.1 ± 2.6	< 0.01**	-5.0 ± 3.0	-4.0 ± 2.5	0.44
post ΔeGFR (ml/min/1.73m^2/year)	-0.3 (-2.4-2.9)	-4.1(-6.2-3.7)	< 0.01**	-2.6 ± 4.0	-1.6 ± 2.8	0.52
ΔΔeGFR (ml/min/1.73m^2/year)	-6.6 ± 5.3	-2.0 ± 1.0	< 0.01**	2.4 ± 5.7	2.5 ± 4.6	0.98
pre ΔTKV（%/year）	9.5 (5.6-14.4)	9.9 (7.2-14.7)	0.68	12.8 ± 8.0	8.2 ± 3.9	0.15
post ΔTKV（%/year）	-4.1 ± 10.3	-3.9 ± 16.5	0.96	-10.7 ± 9.2	8.5 ± 9.5	< 0.01**
ΔΔTKV（%/year）	-14.3 ± 9.7	-16.3 ± 21.5	0.78	-19.6 (-23.7--17.3)	-1.8(-6.1-0.4)	< 0.01**

Data are presented as mean ± standard deviation, as number (%) or as median (interquartile range) if skewed. [a]Data are shown at hospitalization for tolvaptan administration. [b]TKV 1 year after tolvaptan initiation were not measured in 1 patient, thus statistical analysis of ΔΔTKV was performed in total 23 patients. *P* value was calculated with student's *t*-test in parametric variables or Mann -Whitney's U test was used in non-parametric variables. ADPKD, Autosomal dominant polycystic kidney disease ; BP, blood pressure ; eGFR, estimated glomerular filtration rate ; TKV, total kidney volume ; BSA, body surface area.

< -5%/year. The responders in ΔΔeGFR (N = 14) presented a significant difference in proteinuria (p < 0.05*), pre ΔeGFR (*p* < 0.01**), post ΔeGFR (*p* < 0.01**), and ΔΔeGFR (*p* < 0.01**). With respect to ΔΔTKV, the responders (N = 15) showed a significant difference in post ΔTKV (*p* < 0.01**) and ΔΔTKV (*p* < 0.01**). There was no difference in blood pressure, TKV, eGFR, or urine osmolality between the responders and the non-responders. Interestingly, these data indicated that the effect of tolvaptan on eGFR and TKV was independent and that the rate of eGFR change before treatment may be the index of responder in eGFR.

Correlation of ΔΔeGFR or ΔΔTKV with clinical characteristics in the responder group

Furthermore, we examined the correlated factors with ΔΔeGFR or ΔΔTKV in the responders (Table 3). ΔΔeGFR significantly correlated with proteinuria (ρ = -0.36, p < 0.05*), eGFR at tolvaptan initiation (ρ = 0.77, p < 0.01**), TKV at tolvaptan initiation (ρ = -0.59, p < 0.05*), pre ΔeGFR (ρ = -0.91, p < 0.01**), and post ΔeGFR (ρ = 0.75, p < 0.01**) in the ΔΔeGFR responder group, wherein eGFR at tolvaptan initiation was significantly correlated with TKV at tolvaptan initiation (ρ = -0.78, p < 0.01**). ΔΔTKV showed significant correlation with hypertension history

Table 3. Correlation of ΔΔeGFR and ΔΔTKV with clinical characteristics

	ΔΔeGFR responder (N = 14)		ΔΔTKV responder (N = 15)	
	ρ	*p* value	ρ	*p* value
Age	-0.03	0.91	0.01	0.98
Male	0.28	0.67	0.08	0.81
family history of ADPKD	-0.28	0.40	0.58	0.08
hypertension history[a]	0.32	0.54	0.67	< 0.05*
liver cyst[a]	0.13	0.27	0.56	0.16
cerebral aneurysm[a]	0.29	0.39	0.56	0.16
proteinuria[a]	-0.36	< 0.05*	0.65	< 0.05*
systolic Bp[a]	-0.16	0.47	0.40	0.15
diastolic BP[a]	-0.05	0.82	0.16	0.60
eGFR[a]	0.77	< 0.01**	-0.45	0.09
TKV[a]	-0.59	< 0.05*	0.63	< 0.05*
urine volume[a]	0.29	0.29	-0.02	0.90
urine osmolality	-0.28	0.31	-0.19	0.49
BSA-corrected tolvaptan dosage	0.25	0.37	-0.08	0.74
pre ΔeGFR	-0.91	< 0.01**	-0.20	0.46
post ΔeGFR	0.75	< 0.01**	0.01	0.96
ΔΔeGFR	-	-	0.28	0.30
pre ΔTKV	-0.35	0.20	0.08	0.78
post ΔTKV	-0.37	0.19	0.76	< 0.01**
ΔΔTKV	-0.11	0.70	-	-

P value is calculated with spearman's correlation coefficient test by rank test. ADPKD, Autosomal dominant polycystic kidney disease ; BP, blood pressure ; eGFR, estimated glomerular filtration rate ; TKV, total kidney volume ; BSA, body surface area.

(ρ = 0.67, p < 0.05*), proteinuria (ρ = 0.65, p < 0.05*), TKV at tolvaptan initiation (ρ = 0.63, p < 0.05*), and post ΔTKV (ρ = 0.76, p < 0.01**) in the ΔΔTKV responder group. In this group, TKV significantly correlated with eGFR (ρ = -0.70, p < 0.01**).

DISCUSSION

This longitudinal observational study investigated the clinical characteristics of the 1-year therapeutic efficacy of tolvaptan in Japanese patients with ADPKD. Our study enrolled patients with a wide range of kidney function, CKD stage 2-4, and evaluated the treatment effect of tolvaptan as ΔΔeGFR or ΔΔTKV before and 1 year after tolvaptan administration, wherein we examined clinical factors associated with tolvaptan efficacy. The current study revealed that pre ΔeGFR was very relevant to the efficacy of tolvaptan on kidney function. In the ΔΔeGFR responder group, the mean pre ΔeGFR was significantly lower and pre ΔeGFR was significantly correlated with ΔΔeGFR, thus suggesting that ADPKD patients with rapid GFR decline clinically show a good response to tolvaptan. The poor prognostic markers of kidney function in ADPKD have been reported as follows : PKD1 gene mutation, younger age at diagnosis, male gender, hypertension, increased left ventricular mass, three or

more pregnancies, and the development of gross hematuria at a younger age (10, 11). The TEMPO trial revealed that tolvaptan was more effective in patients with PKD1 mutation compared to that in patients with PKD2 mutation. These data indicate that patients with PKD1 mutation have poor kidney prognosis but have better response to tolvaptan. The ΔΔeGFR responder group with rapid decline of GFR in the current study may be patients with PKD1 mutation, although we did not examine their genotype. Genotype analyses in ADPKD patients are out of the application range of health insurance treatment in Japan ; thus, pre ΔeGFR may be a predictive factor of therapeutic efficacy on GFR in a practical clinic setting.

Furthermore, ΔΔeGFR in the responder group was positively correlated with eGFR at tolvaptan initiation and negatively correlated with TKV at tolvaptan initiation, wherein eGFR and TKV at tolvaptan initiation showed the significant inverse correlation. In ADPKD, kidney enlargement due to cyst development results in the decline of GFR. These data mean that the effect of tolvaptan on kidney function decreases in patients with late-stage ADPKD. Meiher et al reported that initiation of vasopressin V2 receptor antagonist at an advanced stage of disease lacked renoprotective effects in the Pkd1-deletion mouse model (12). In patients with advanced ADPKD, Tolvaptan has presumably less effect on GFR because of the loss of functional nephron or thick-walled cyst surrounded by irreversible interstitial fibrosis with an associated decline in GFR (13). The results suggest that tolvaptan may have greater efficacy on GFR in early-stage ADPKD with rapid GFR decline.

No predicting factor for the effect on TKV was identified. However, ΔΔTKV presented positive correlation with TKV at tolvaptan initiation in the responder group. The data suggest that patients with early-stage ADPKD have a better response for TKV reduction in the first year of treatment. Interestingly, this trend was also observed in the effect on GFR although the efficacy of tolvaptan on eGFR and on TKV were independent in this study. In the TEMPO 3 : 4 and TEMPO 4 : 4, the treatment effect on TKV reduction was greater in the first year of treatment than in the second and third years. The reduction in TKV during the first year is thought to be due to inhibition of fluid secretion into cysts. Two short-term trials in patients with decreased GFR support this possible mechanism of inhibited fluid secretion. Irazabal et al demonstrated that the administration of tolvaptan over 1 week significantly reduces kidney and cyst volume to a greater extent than it reduces body water without a significant change in renal blood flow in 20 patients with ADPKD with mean eGFR 69.3 ± 34.8 ml/min/1.73m^2, and that the decrease is greater in those with eGFR > 60 ml/min/1.73m^2 than in those with eGFR < 60 ml/min/1.73m^2 (14). In 27 patients with measured GFR ranging from 18 to 148 ml/min, Boertien et al showed that 3 weeks of therapy resulted in a similar decline in TKV that is greater in those with higher kidney function. In addition, in that study, they also showed that free-water clearance per single nephron was greater in patients with decreased kidney function, thus indicating that tolvaptan is pharmacodynamically effective throughout a wide range of kidney function in ADPKD (15). In the current study, eGFR in the ΔΔTKV responder group ranged from 17 to 77 ml/min/1.73m^2. These data suggest that the effect of tolvaptan on TKV in the first year can be obtained in those with a wide range of GFR depending on the number of residual nephrons probably due to the inhibition of fluid secretion.

The current study revealed that the effect of tolvaptan on ΔΔTKV was significantly better in patients without hypertension history at tolvaptan initiation in the ΔΔTKV responder group ($p < 0.05$*). Patients with ADPKD often develop hypertension, presumably because of activation of renin-angiotensin-aldosterone system (RAAS) or endothelial injury (16). RAAS activation in ADPKD is assumed to accelerate renal cyst growth or fibrosis (17, 18). In addition, rigorous BP control is associated with a slower increase in total kidney volume (19). These results indicate that treatment with tolvaptan and anti-hypertensive therapy may additively inhibit cyst enlargement.

Previous studies have reported proteinuria in ADPKD was associated with poor kidney function (20) and kidney enlargement (11). In this study, patients with proteinuria showed poor efficacy of tolvaptan both on GFR and on TKV. However, the current study revealed that those with proteinuria showed the significant low eGFR and the significant large TKV which suggest late-stage ADPKD. We speculate that patients with proteinuria may present poor efficacy due to advanced ADPKD stage.

This study had certain limitations. First, the number of participants is relatively small. However, the current study revealed a significant correlation between tolvaptan efficacy and a few clinical factors, which is in line with published literature. Second, the current study examined 1-year tolvaptan efficacy. The study about long term efficacy is required for suppression of end-stage kidney disease.

The current study revealed the clinical features of tolvaptan effect in ADPKD with a wide range of GFR (CKD stage 2-4). We consider that the annual eGFR change before tolvaptan treatment may be a useful marker of tolvaptan efficacy on kidney function and that tolvaptan should be administered in early-stage ADPKD with rapid GFR decline under sufficient BP control. We consider that our data contribute the efficient use of tolvaptan in ADPKD in practical clinic settings. Future studies with a greater number of patients could provide more significant results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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