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Long-Term Outcomes of Longitudinal Efficacy Study With Tolvaptan in ADPKD

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Introduction: The effects of long-term and uninterrupted tolvaptan treatment on autosomal dominant polycystic kidney disease (ADPKD) are unclear. Therefore, a more than 3-year continuous treatment study was performed.

Methods: From the Kyorin University cohort, 299 patients were surveyed and 179 patients were indicated for tolvaptan having a total kidney volume (TKV) ≥750 ml, TKV slope ≥5%/yr, and estimated glomerular filtration rate (eGFR) ≥15 ml/min per 1.73 m^2. Among 179 patients, 118 patients consented to the study.

Results: Retrospective pretreatment and prospective on-treatment periods had a median of 1.8 and 4.0 years, respectively. During the 5 treatment-years, the $\log_{10}$(TKV) slope/yr decreased from the pretreatment period ($P < 0.0001$) and the estimated height-adjusted TKV growth rate α (eHTKV-α, %/yr) decreased from baseline ($P < 0.0001$). The decline in eGFR improved in female patients ($P < 0.0001$), but not in males ($P = 0.6321$). Furthermore, during the 5 treatment-years, eGFR remained significantly better in the group with a percent decrease in eHTKV-α from baseline to the first treatment-year ≥ the median (2.94%) than in the group with a decrease <2.94%. The free-water clearance was higher in males than in females irrespective of treatment.

Conclusion: The TKV growth rate decreased in 4 years with tolvaptan in both sexes. The insignificant effects of tolvaptan on the eGFR slope in males were likely due to androgen stimulation of cystogenesis and analytical difficulty of longitudinal changes in nonlinear trajectories of eGFR. The larger decrease in eHTKV-α in the first year was related to a better renal prognosis. The vasopressin-mediated water reabsorption was activated more in females than males irrespective of tolvaptan administration.

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ADPKD is characterized by progressive enlargement of the kidney resulting from the formation and expansion of renal cysts and is associated with the deterioration of kidney function.[1–3] Increased levels of 3′- to 5′-cyclic adenosine monophosphate (cAMP) in the renal tubular cells and abnormal stimulation of vasopressin V2-receptor (V2R) play a central role in cystogenesis.[4,5]

The Tolvaptan Efficacy and Safety in Management of ADPKD and its Outcomes (TEMPO) 3:4 study revealed the efficacy of tolvaptan, a selective V2R antagonist, in slowing the increase in TKV and the decline in kidney function in 3 years.[6] In the TEMPO 3:4 study, a greater decrease in TKV enlargement was observed during the first year than during the second and third years, which raised concerns on its long-term efficacy. Although the long-term efficacy of tolvaptan was reported in 2 studies,[7,8] tolvaptan treatment was interrupted between completion of the preceding 3-year TEMPO 3:4 study and initiation of the next 2-year TEMPO 4:4 study from 13 to 829 days,[7] and participants were retrospectively collected from different clinical trials.[8] In fact, TKV slopes in TEMPO 4:4 were

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even higher in early- compared with delayed-treated subjects (6.16 vs. 4.96%/yr, $P < 0.05$), and prespecified noninferiority could not be established. The effects of tolvaptan in TKV growth may be blunted in subjects who resume treatment after a prolonged interruption,[7] and the efficacy of continuously administered tolvaptan on TKV growth remains inconclusive.

The vasopressin-cAMP-osmolality axis is abnormal in ADPKD.[4,9] Patients with ADPKD exhibited a significant defect both in the release of vasopressin and in the V2R-mediated renal osmotic response.[10] The expression of V2R mRNA, its protein, and aquaporin 2 was higher in female non-PKD rats than in male non-PKD rats.[11,12] Nevertheless, sex differences in V2R-mediated water homeostasis and its response to tolvaptan are not well reported in patients with ADPKD.

Therefore, the effects of tolvaptan on the increase in TKV and decrease in the eGFR were evaluated for up to 5 years using a 1-group pretreatment versus on-treatment design. Concomitantly, the relationship between changes in the eHTKV-α from baseline and changes in eGFR[13] and sex differences in water homeostasis was evaluated.

METHODS

Study Design

The Longitudinal Efficacy and Safety Study of Tolvaptan on ADPKD study was an observational study using a 1-group pretreatment versus on-treatment design to evaluate the effects of continuously administered tolvaptan on the TKV growth rate and eGFR decline rate for 5 years.

The study protocol was approved by the institutional review board of Kyorin University (744-09) and registered in ClinicalTrials.gov (identification NCT02729662) and UMIN-CTR (identification UMIN000021267). All enrolled patients provided written informed consent.

Study End Points

The primary end point was the effects of the 5-year tolvaptan treatment on the TKV growth rate, and the secondary end point was its effects on the eGFR decline rate. The slope of TKV was analyzed by fitting it to $\log_{10}$(TKV).[6] The effects of tolvaptan were analyzed by the subclasses with sex difference and *PKD* genotypes. Other end points included the safety of tolvaptan and its effects on free-water clearance.

Study Participants and Sample Size Calculation

In 2014, tolvaptan was approved in Japan for the treatment of patients with ADPKD with the official criteria of TKV $\geq$750 ml, TKV growth rate $\geq$5%/yr, and eGFR $\geq$15 ml/min per 1.73 m^2. Participants were recruited from adult patients who visited Kyorin University Hospital and consented to tolvaptan treatment between May 2014 and March 2017. The final data collection was August 2020 (Figure 1). The TKV growth rate measured on a year-to-year basis fluctuated considerably,[14] and subjects with an average TKV growth rate <5%/yr may have been included in this study.

Participants in TEMPO 3:4 were not included to avoid influences of the preceding tolvaptan treatment and its interruption.[7] Patients with interrupted tolvaptan intake for >1 month were excluded from the study.

We calculated 100 patients to be necessary assuming a $\log_{10}$(TKV) slope of 5.5%/yr and 2.8%/yr for pretreatment and on-treatment, respectively (Supplementary Table S1).

Method of Treatment and Data Collection

Tolvaptan administration was initiated during the 3-day hospitalization with the standard starting dose being a daily split dose of 45 mg/15 mg. For subjects weighing <50 kg or aged >65 years, the starting dose was reduced to 30 mg/15 mg. During the treatment period, the dose was increased up to 90 mg/30 mg or reduced as tolerated. Natural or filtered water was recommended to drink because of contaminated chlorine metabolites in tap water.[15]

TKV was measured using a standard protocol for magnetic resonance imaging without contrast medium.[3] As a cohort study, TKV and 24-hour urine were measured basically once a year,[3] and these data were used as retrospective data. The baseline TKV, 24-hour urine, and eGFR were measured within 1 month before the initiation of tolvaptan treatment. During the on-treatment period, TKV was measured every year ($\pm$1 month) or before withdrawal ($\pm$2 month) and 24-hour urine was collected twice a year using the "Sumius U-Container" (Sumitomo Bakelite, Tokyo, Japan). Serum liver enzymes and eGFR were measured monthly. eGFR data fluctuated owing to unstable hydration during the initial 1 week and were not used for analysis. The modified IDMS–MDRD Study equation with the Japanese coefficient 0.808 was used for eGFR calculation.[16] Protein intake was estimated using 24-hour urine data by Maroni's equation.[17]

DNA Analyses

PKD1 and *PKD2* target sequencing was performed using genomic DNA on a MiSeq sequencer (Illumina, San Diego, CA) and MLPA (SALSA MLPA: MRC Holland, Amsterdam, The Netherlands). The variants were confirmed by direct Sanger sequencing of

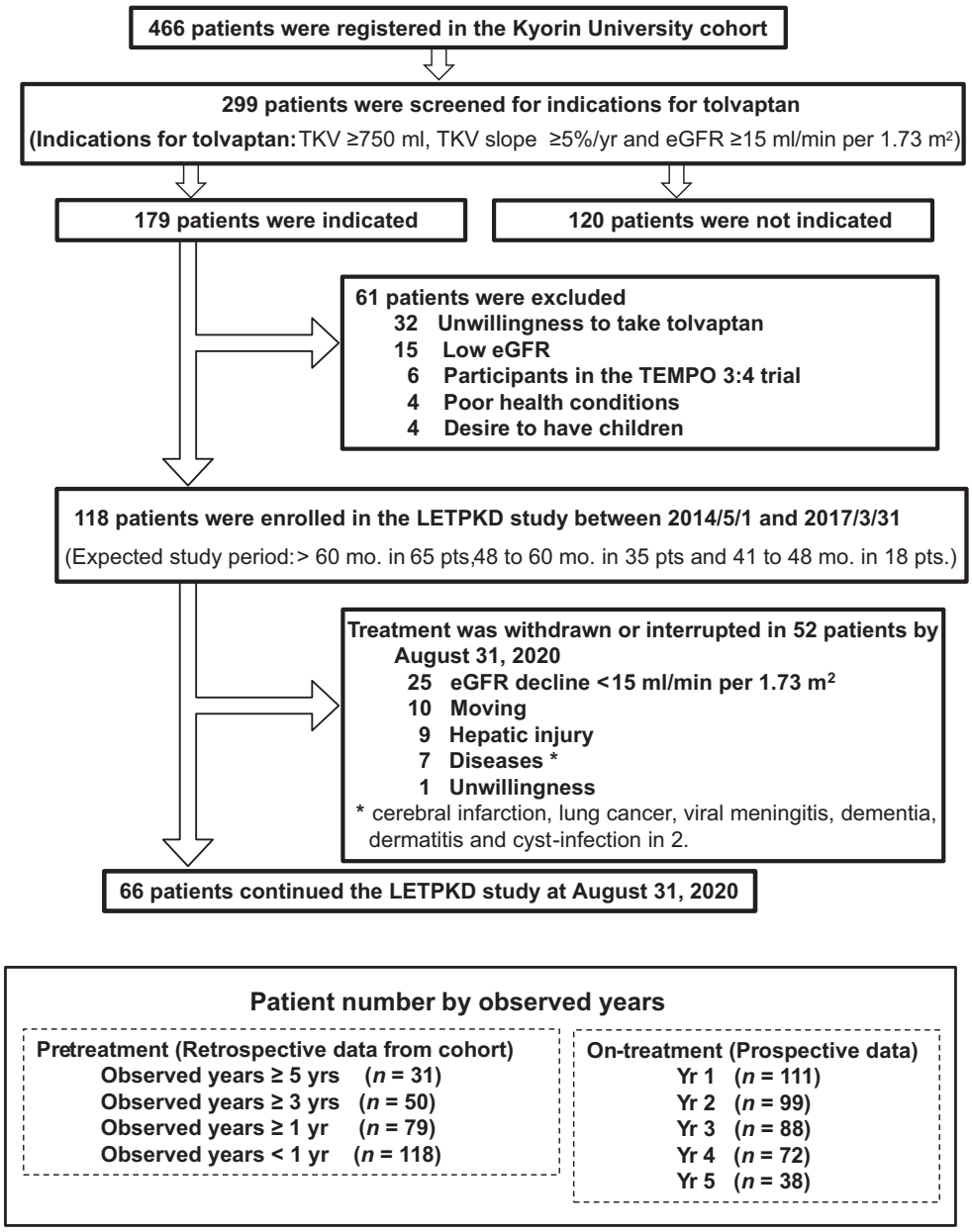

Figure 1. Outline of the longitudinal 1-group study design with the pretreatment cohort study and on-treatment prospective study. TKV was usually measured yearly. Expected study period was that from study entry date to August 31, 2020. eGFR, estimated glomerular filtration rate; mo, month; pt, patient; TEMPO, Tolvaptan Efficacy and Safety in Management of ADPKD and its Outcomes; TKV, total kidney volume.

genomic DNA. Pathogenic variations were confirmed according to MutationTester, PROVEAN, and Polyphen-2.[18] The institutional ethical committees approved the DNA protocol, and DNA-specific consent was received from all participants.

Estimated HTKV Growth Rate α

The eHTKV-α originates from the Mayo Class[19] and was calculated by the following equation: $HTKVt = K(1 + eHTKV\text{-}\alpha / 100)^t$, where HTKVt is HTKV at age t and K is HTKV at age 0. The equation constant K was corrected from 150 ml/m used in the Mayo Class to 130 ml/m to stabilize the eHTKV-α. The decrease in eHTKV-α from baseline implies treatment effects on the HTKV growth rate[13] and was used for prespecified and additional analytical methods.

Statistical Methods

Normally distributed variables were expressed as mean ± SD or SE. Differences between groups were tested using the χ^2 test for categorical variables, and a general linear mixed-effect model with covariates as factors was used for continuous variables. The observed year-specific curves of $\log_{10}$(TKV) and eGFR slopes analyzed using a generalized additive model were used to identify covariates for major end point analysis (Supplementary Figure S2A and B). Changes in eHTKV-α from baseline to treatment-years were compared

Table 1. Baseline demographic and clinical characteristics of patients according to treatment-years

Characteristics	Enrolled (total)	Continuous treatment-years					*P* value
		Year 1	Year 2	Year 3	Year 4	Year 5	
Patient number	118	111	99	88	72	38	
Percentage of male (%) (male/female)	45.8 (54/64)	45.9 (51/60)	47.5 (47/52)	44.3 (39/49)	41.7 (30/42)	42.1 (16/22)	0.9450
Median observed years before treatment (95% CI)	1.8 (2.43–3.38)	1.8 (2.3–3.3)	1.8 (2.4–3.4)	1.8 (2.4–3.5)	2.8 (2.7–3.9)	3.2 (2.5–4.2)	—
Observed years before treatment	2.90 ± 2.59	2.81 ± 2.49	2.88 ± 2.50	2.93 ± 2.52	3.27 ± 2.58	3.39 ± 2.54	0.4306
Median treatment-years (95% CI)	4.0 (3.50–4.12)	1 (0.91–0.96)	2 (1.92–1.96)	3 (2.93–2.96)	4 (3.9–3.9)	5 (4.9–5.0)	—
Treatment-years	3.8 ± 1.7	0.9 ± 0.1	1.9 ± 0.1	2.9 ± 0.1	3.9 ± 0.1	4.9 ± 0.1	—
Age at enrollment (yr)	51.7 ± 12.3	51.6 ± 12.4	51.1 ± 12.6	50.3 ± 12.7	50.1 ± 13.3	49.6 ± 12.5	0.8945
Baseline age group, *n*, (%)							
20–49 yr	61 (51.7)	58 (52.3)	54 (58.3)	51 (58.0)	42 (58.3)	25 (65.8)	0.9301
50–59 yr 60–79 yr	28 (23.7) 29 (24.6)	26 (23.4) 27 (24.3)	21 (21.2) 24 (24.2)	18 (20.5) 19 (21.6)	13 (18.1) 17 (23.6)	5 (13.2) 8 (21.1)	
Tolvaptan dose per body weight (mg/kg/d)	0.995 (0.397)	1.057 (0.318)	1.068 (0.326)	1.068 (0.035)	1.101 (0.343)	1.183 (0.362)	0.3252
Baseline eGFR (ml/min per 1.73 m^2)	47.1 ± 20.4	47.6 ± 20.5	49.5 ± 19.7	51.5 ± 19.2	52.9 ± 19.6	55.1 ± 19.1	0.2055
Baseline CKD stage, *n* (%)							
1 and 2 (eGFR ≥60)	34 (28.8)	33 (29.7)	31 (31.3)	30 (34.1)	27 (37.5)	16 (42.1)	0.4791
3a (eGFR 45–59) 3b (eGFR 30–44) 4 (eGFR 15–29)	23 (19.5) 33 (28.0) 28 (23.7)	23 (20.7) 30 (27.0) 25 (22.5)	23 (23.2) 26 (26.3) 19 (19.2)	20 (22.7) 25 (28.4) 13 (14.8)	16 (22.2) 20 (27.8) 9 (12.5)	7 (18.4) 14 (36.8) 1 (2.6)	
Baseline TKV (ml)	2153 ± 943	2173 ± 951	2146 ± 966	2092 ± 891	2117 ± 890	1993 ± 962	0.8750
Baseline HTKV (ml/m)	1305 ± 556	1319 ± 561	1302 ± 568	1274 ± 534	1292 ± 537	1209 ± 574	0.8696
Baseline eHTKV-α (%/yr)	4.64 ± 1.43	4.68 ± 1.45	4.71 ± 1.50	4.76 ± 1.51	4.84 ± 1.56	4.61 ± 1.10	0.9397
Height (cm)	164.7 ± 9.6	164.4 ± 9.2	164.4 ± 9.5	164.1 ± 9.5	163.9 ± 9.8	165.0 ± 10.2	0.9807
Weight (kg)	63.7 ± 13.4	63.8 ± 13.5	64.1 ± 13.8	64.0 ± 14.2	63.4 ± 14.3	63.0 ± 12.7	0.9926
Systolic blood pressure (mm Hg)	129.4 ± 18.2	129.4 ± 18.5	129.7 ± 19.1	130.6 ± 19.6	130.4 ± 19.9	130.7 ± 19.3	0.9917
Diastolic blood pressure (mm Hg)	81.7 ± 12.3	81.7 ± 12.6	81.8 ± 12.5	82.7 ± 12.8	82.9 ± 13.1	83.9 ± 12.9	0.8808
Medication for HTN, with, (%)	105 (89.0)	99 (89.2)	88 (88.9)	78 (88.6)	63 (87.5)	32 (84.2)	0.9408
Genotype, *n* (%)							
PKD1 truncating	53 (44.9)	51 (45.9)	46 (46.5)	40 (45.5)	34 (47.2)	17 (44.7)	0.9936
PKD1 nontruncating *PKD2* Mutation unidentified or no test	37 (31.4) 14 (11.9) 14 (11.9)	34 (30.6) 14 (12.6) 12 (10.8)	34 (34.3) 11 (11.1) 8 (8.1)	31 (35.2) 11 (12.5) 6 (6.8)	25 (34.7) 8 (11.1) 5 (6.9)	15 (39.5) 3 (7.9) 3 (7.9)	
Positive family history, with (%)	81 (68.6)	78 (70.3)	69 (69.7)	62 (70.5)	52 (72.2)	26 (68.4)	0.9998
Age at diagnosis of ADPKD (yr)	38.9 ± 12.4	38.5 ± 12.4	38.1 ± 12.3	37.9 ± 12.4	36.7 ± 13.1	37.8 ± 12.6	0.9171
Age at initial manifestation (yr)	36.4 ± 11.8	36.5 ± 12.0	35.9 ± 11.6	35.3 ± 11.4	34.7 ± 12.2	36.7 ± 10.5	0.8520

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; eHTKV-α, estimated height-adjusted total kidney volume growth rate α; HTKV, height-adjusted total kidney volume; HTN, hypertension; TKV, total kidney volume.
eHTKV-α calculated by the eHTKV-α equation.[17] Data are the mean ± SD or median value for numerical variables and patient number for categorical variables. Tolvaptan dose is that during the first year of treatment. *P* values were for 5 continuous treatment-year groups and derived from analysis of variance for numeric variables and the χ^2 test (Pearson) for categorical variables.

using a mixed-effect model. Analyses were performed using SAS 9.4 and JMP Pro 14.3.0. A 2-sided $P < 0.05$ was considered significant.

RESULTS

Baseline Clinical Characteristics of Participants

The Longitudinal Efficacy and Safety Study of Tolvaptan on ADPKD study enrolled 118 patients. The expected study period, from the start date of tolvaptan to the end of the observation (August 31, 2020), was longer than 60 months in 65 patients, 48 to 60 months in 35 patients, and 41 to 48 months in 18 patients. Major reasons of withdrawal were eGFR decline < 15 ml/min per 1.73 m^2, moving, drug-induced hepatic injury, and tolvaptan-unrelated diseases (Figure 1). Drug-induced hepatic injury mostly developed in the first year, but other adverse events or events requiring study termination developed throughout the treatment period.

The mean pre- and on-treatment observation periods were 2.9 ± 2.6 and 3.8 ± 1.7 (SD) years, respectively (Table 1). The clinical characteristics of the patients at baseline were not significantly different among the 5 treatment-year groups (Table 1). In males, the baseline age was slightly younger, and the baseline eHTKV-α and percentage with hypertension medication and unknown family history were significantly higher than in females (Supplementary Table S2).

Primary End Point: Tolvaptan Effects on the TKV Growth

The individual trajectories of $\log_{10}$(TKV) and eGFR were plotted against pre- and on-treatment-years (Supplementary Figure S1A and B). Age and sex were

Table 2. Changes in slopes of $\log_{10}$(TKV) and eGFR with treatment and its sex comparison

Slope of $\log_{10}$(TKV)/yr							
		Pretreatment		On-treatment		Difference	
Category	N	Mean ± SE	95% CI	Mean ± SE	95% CI	Mean ± SE	*P* value
Total	118	0.0182 ± 0.0015	0.0152–0.0212	0.0125 ± 0.0014	0.0097–0.0154	−0.0056 ± 0.0011	<0.0001
Sex							
Male	54	0.0223 ± 0.0022	0.0180–0.0266	0.0179 ± 0.0020	0.0180–0.0266	−0.0044 ± 0.0016	0.0060
Female	64	0.0150 ± 0.0020	0.0111–0.0189	0.0081 ± 0.0019	0.0044–0.0117	−0.0069 ± 0.0015	<0.0001
Difference[a]		–	–	–	–	0.0026 ± 0.0022	0.2391
Slope of eGFR/yr							
		Pretreatment		On-treatment		Difference	
Category	N	Mean ± SE	95% CI	Mean ± SE	95% CI	Mean ± SE	*P* value
Total	118	−4.08 ± 0.18	−4.44 to −3.73	−3.46 ± 0.16	−3.78 to −3.14	0.62 ± 0.12	<0.0001
Sex							
Male	54	−3.53 ± 0.27	−4.07 to −2.99	−3.62 ± 0.24	−4.09 to −3.14	−0.09 ± 0.19	0.6321
Female	64	−4.41 ± 0.24	−4.88 to −3.94	−3.36 ± 0.22	−3.80 to −2.92	1.05 ± 0.15	<0.0001
Difference[a]		–	–	–	–	−1.14 ± 0.24	<0.0001

eGFR, estimated glomerular filtration rate (ml/min per 1.73 m^2); TKV, total kidney volume (ml).
[a]Compares difference of treatment effect in the slope of $\log_{10}$(TKV) and eGFR between sexes.
Slopes for total kidney volume were analyzed by fitting to the $\log_{10}$-transformed TKV. The slopes of $\log_{10}$(TKV) and eGFR were analyzed using the mixed effects models with age, the categories, time A (pretreatment and on-treatment) by the category interaction and time B (on-treatment) as fixed effects, with intercept and time A by the category interaction as fixed effects with unknown correlation.

adopted as covariates for major end point analyses according to the generalized additive model analysis (Supplementary Figure S2). The $\log_{10}$(TKV) slope decreased significantly ($P < 0.0001$) with tolvaptan treatment (Table 2). The decrease in $\log_{10}$(TKV) slope with tolvaptan was not different between sexes ($P = 0.2391$).

The on-treatment mean $\log_{10}$(TKV) (A in Table 3) decreased from the pretreatment estimated mean $\log_{10}$(TKV) (B in Table 3) in the 5-year period ($P < 0.0001$). Changes in TKV from the previous year decreased in the first year (1.27%) and thereafter remained almost constant from 2 to 5 years (Table 3 and Figure 2).

The $\log_{10}$(TKV) slopes at pre- and on-treatment periods were similar between the analysis with and without adjustment by sex and age (Table 2 and Supplementary Table S3).

The treatment effects on the TKV growth rate in the 5-year period were also verified by the decrease in eHTKV-α from baseline (Supplementary Table S4). In females, the eHTKV-α significantly decreased from baseline for 5 treatment-years, but the decrease was not significant in males at 3 and 5 treatment-years. Sex differences were significant at 3 years ($P = 0.0384$) (Supplementary Table S4).

Secondary End Point: Tolvaptan Effects on the eGFR Slope

The eGFR slope was significantly improved by tolvaptan in females, but not in males. The difference in effects on the eGFR slope was significant between the sexes ($P < 0.0001$; Table 2).

PKD Mutation Types and Tolvaptan Effects on the TKV Slope

Distribution of pathogenic *PKD* mutations is summarized in Supplementary Table S5. The $\log_{10}$(TKV) slope decreased with tolvaptan treatment irrespective of *PKD* mutation types (Table 4 and Figure 3). The decrease in the $\log_{10}$(TKV) slope was significantly larger ($P = 0.0247$) in subjects with *PKD2* mutation than in those with *PKD1*-truncating type mutation.

Renal Osmotic Responses to Tolvaptan and Comparison of Water Handling Between the Sexes

The age at enrollment, baseline eGFR, and tolvaptan dose were not different between the sexes (Supplementary Table S2). At baseline, serum osmolality, urine volume, and free-water clearance were lower in females than in males, suggesting higher solute-free-water reabsorption in females (Table 5). With tolvaptan, the urine volume, free-water clearance, serum osmolality, and serum sodium concentration increased, whereas the urine osmolality decreased in both sexes. The qualitative differences between sexes noted at baseline in serum osmolality, urine volume, and free-water clearance were maintained throughout tolvaptan treatment, suggesting sustained enhanced free-water reabsorption in females (Table 5 and Figure 4).

The 24-hour urinary excretion of electrolytes, protein, albumin, β2-microglobulin, and N-acetyl-β-D-glucosaminidase and protein intake estimated by 24-hour urine were not different between sexes or

Table 3. The estimation of treatment effects of tolvaptan on mean $\log_{10}$(TKV) for each year

	On-treatment					Estimated pretreatment					Change in TKV from previous year			
	$\log_{10}$(TKV)			TKV (ml)		$\log_{10}$(TKV)			TKV (ml)		Pre-Tx		On-Tx	
Pre- and on-Tx year	Estimated mean (A)	95% CI	SE	Estimated mean	95% CI	Estimated mean (B)	Tx effect (B)–(A)	95% CI	Estimated mean	*P* value	(ml)	(%)	(ml)	(%)
−5	3.176	3.140–3.213		1501	1380–1633	3.190			1549					
−4	3.215	3.179–3.251		1640	1510–1781	3.211			1627					
−3	3.238	3.203–3.273		1729	1594–1876	3.232			1708					
−2	3.261	3.226–3.296		1824	1683–1977	3.254			1793					
−1	3.278	3.244–3.313		1897	1753–2054	3.275			1882					
BL	3.295	3.261–3.330		1974	1825–2135	3.296			1976					
1	3.290	3.255–3.324	0.004	1949	1801–2110	3.317	0.027	0.019–0.053	2075	<0.0001	99	5.01	−25	−1.27
2	3.306	3.271–3.340	0.004	2022	1868–2190	3.338	0.032	0.024–0.063	2178	<0.0001	103	4.96	73	3.54
3	3.329	3.294–3.363	0.004	2131	1967–2307	3.359	0.031	0.022–0.060	2287	<0.0001	109	5.00	108	4.96
4	3.347	3.312–3.382	0.005	2222	2051–2407	3.380	0.034	0.024–0.066	2401	<0.0001	114	4.98	91	3.99
5	3.370	3.335–3.406	0.006	2346	2161–2546	3.401	0.031	0.019–0.061	2502	<0.0001	101	4.21	124	5.16

BL, baseline; TKV, total kidney volume; Tx, treatment.
The pretreatment mean $\log_{10}$(TKV) was estimated by a regression line analyzed using pretreatment data (B). The on-treatment mean $\log_{10}$(TKV) was estimated using pre- and on-treatment data (A) (Figure 2). Data were analyzed by the linear mixed-effect model with fixed effects of age, sex, and treatment-year. *P* value is for the difference in mean $\log_{10}$(TKV) of (B) and (A) calculated by (B)–(A) and SE of the estimated mean. TKV was converted from $\log_{10}$(TKV).

between pre- and on-treatment periods (Supplementary Table S6).

Changes in eHTKV-α From Baseline to the First Treatment-Year Associated With eGFR Decline

The relationship between the changes in TKV and eGFR was evaluated. As direct individual comparison of TKV change was found to yield considerable bias,[14] the quantitative extent of TKV change with tolvaptan was estimated by the percent change in eHTKV-α from baseline.[13] The median of the percent change was −2.94%, with a first and third quartile of −0.78% and −5.40%, respectively. The subjects with a decrease ≥2.94% were termed good responders and those with a decrease <2.94% or an increase in eHTKV-α from baseline were termed poor responders. The changes in eGFR were compared between the 2 responders by treatment-years in patients with baseline CKD stage 1 to 3 (Table 6 and Figure 5). The decline in eGFR was slower in good responders than in poor responders. Nevertheless, the baseline eGFR was lower in poor responders than in good responders and the rapid progression in poor responders may have been influenced by coexisting poorer renal function (Supplementary Table S7).

Adverse Events Related to Tolvaptan

In 9 patients (7.6% of participants), drug-induced liver injury developed between 54 days and 811 days (median of 174 days) after the initiation of tolvaptan. Liver enzyme levels returned to normal after the discontinuation of tolvaptan in all patients. Tolvaptan was discontinued in 9 patients with drug-induced liver injury and in 1 patient with drug-induced dermatitis (Figure 1 and Supplementary Table S8). No patient discontinued tolvaptan owing to aquaresis-related adverse events.

DISCUSSION

This study revealed that tolvaptan can attenuate the TKV increase during continued treatment over 3 years. The average TKV increase of 5%/yr without tolvaptan (Table 3) is consistent with the previous observations[1,6] and the TKV decreased by 1.3% in the first treatment-year. The decrease in TKV in the first year was explained by the decrease in the secretion of cyst fluid.[6] The acute TKV decrease at 1 to 3 weeks observed in short-term tolvaptan studies is consistent with this decrease.[20,21] The significant decrease in $\log_{10}$(TKV) slope from pretreatment to on-treatment (Table 2) and significant decrease in eHTKV-α from baseline during the 5 treatment-years (Supplementary Table S4) suggest the sustained inhibition of cyst

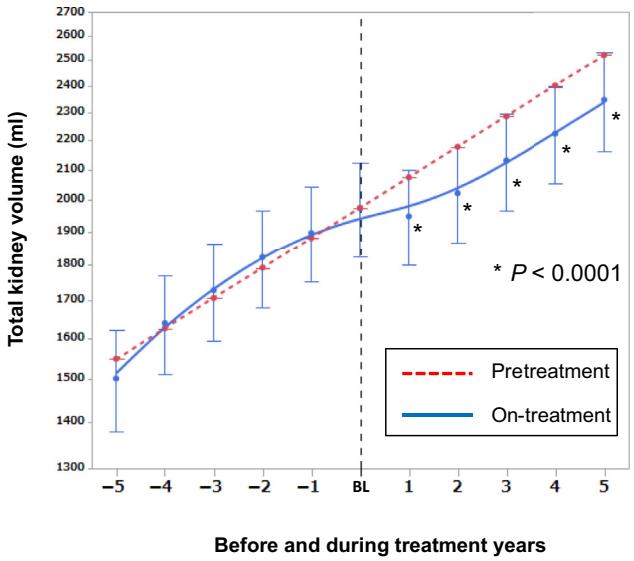

Figure 2. Tolvaptan effects during 5 treatment-years. The red dotted line corresponds to (B) in Table 3; the regression line was estimated by a linear mixed-effect model using $\log_{10}$(TKV) of the pretreatment period. The estimated pretreatment means were extrapolated to the on-treatment period. The blue line corresponds to (A) in Table 3; the mean estimated by a linear mixed-effect model using data during both pretreatment and on-treatment periods. Range is the 95% upper and lower CIs. BL, baseline; TKV, total kidney volume.

fluid secretion and cyst-cell proliferation, which were observed in animal and human cell models.[22,23]

The higher baseline eHTKV-α in males than in females (5.04 vs. 4.31%/yr, $P = 0.0055$ in Supplementary Table S2) suggested a faster TKV increase in males than in females, as reported previously.[4,24] The faster cyst enlargement in males may be explained by testosterone stimulation of cyst fluid secretion by increased cAMP production, as observed in PKD cells[25] and dihydrotestosterone stimulation of signaling pathways downstream of V2R-stimulated cAMP and protein kinase A production, as observed in PKD animal models[26,27] (Supplementary Figure S3A). The effects of tolvaptan to suppress the TKV growth rate, estimated by the changes in eHTKV-α from baseline, were slightly larger in females, but the sex difference was marginal (Table 2 and Supplementary Table S4).

In contrast to the effects of tolvaptan on TKV growth, the beneficial effects on eGFR decline were absent in males (Table 2). As the decline in renal function correlates with the rate of kidney growth,[19,28,29] the effects on TKV growth may improve kidney function decline. Cysts are formed mainly in the collecting ducts and prevent tubular fluid flow from a large number of upstream nephrons.[30] The site and timing of cyst development in the collecting ducts may be random, which may result in dissimilar patterns of eGFR decline. In addition, incidental episodes of cyst infection, gross hematuria, or acute kidney injury damage kidney function to varying extents. These factors may result in complex and individually different trajectories of eGFR decline.[31] The $\log_{10}$(TKV) slope is approximately straight,[1,13] and its changes are fairly sensitive to statistical analysis. In contrast, changes in diverse eGFR trajectories may be difficult to analyze statistically. This may be one of the reasons why the eGFR slope was not different between the low blood pressure group and the standard blood pressure group even though the annual percentage increase in TKV was significantly lower in the low blood pressure group than in the standard blood pressure group in the Halt Progression of Polycystic Kidney Disease Study.[32] In addition, the longitudinal change made it difficult to analyze the change in diverse trajectories of eGFR decline in the present study.

In a subgroup analysis of Japanese patients (118 tolvaptan- and 59 placebo-treated patients) in the TEMPO 3:4 trial, kidney function improved in males, but no effect was observed in females.[33] A small number of patients may yield different results regarding the treatment efficacy on kidney function.

The relationship between changes in TKV and eGFR during treatment were evaluated (Table 6 and Figure 5). Treatment effects on the TKV growth rate were evaluated using the percent change in eHTKV-α

Table 4. Comparison of baseline eHTKV-α and change in $\log_{10}$(TKV) slope with tolvaptan treatment according to *PKD* mutation types

				Slope of $\log_{10}$(TKV)/yr						
		Baseline eHTKV-α		Pretreatment		On-treatment		Difference		
Mutation types	N	Mean ± SE	95% CI	Mean ± SE	95% CI	Mean ± SE	95% CI	Mean ± SE	95% CI	*P* value
PKD1	90	4.82 ± 0.16	4.53–5.12	0.0184 ± 0.0016	0.0152–0.0215	0.0136 ± 0.0015	0.0107–0.0166	−0.0048 ± 0.0012	−0.0071 to −0.0024	<0.0001
PKD2	14	3.40 ± 0.38	2.65–4.15	0.0127 ± 0.0040	0.0048–0.0207	0.0079 ± 0.0021	0.0038–0.0121	−0.0076 ± 0.0015	−0.0106 to −0.0046	<0.0001
PKD1 Tr.	53	4.98 ± 0.19	4.59–5.36	0.0194 ± 0.0021	0.0152–0.0235	0.0162 ± 0.0019	0.0124–0.0200	−0.0032 ± 0.0016	−0.0063 to 0.000	0.0479
PKD1 Non-tr.	37	4.61 ± 0.23	4.15–5.07	0.0171 ± 0.0025	0.0122–0.0220	0.0100 ± 0.0023	0.0055–0.0145	−0.0071 ± 0.0020	−0.0110 to −0.0033	0.0003
PKD2	14	3.40 ± 0.38	2.65–4.15	0.0164 ± 0.0017	0.0130–0.0198	0.0095 ± 0.006	0.0063–0.0127	−0.0069 ± 0.0012	−0.0093 to −0.0044	<0.0001

Non-tr., nontruncating; TKV, total kidney volume; Tr., truncating.
The slope of TKV was analyzed by a linear mixed-effect model by fitting TKV to $\log_{10}$(TKV) with fixed effects of age, sex, mutation type, whole TKV measurement year and year during tolvaptan treatment, and interaction sex*whole measurement year, sex × year during tolvaptan treatment, mutation type*whole measurement year, and mutation type × year during tolvaptan treatment. *P* values compare the $\log_{10}$(TKV) slope between pre- and on-treatment.

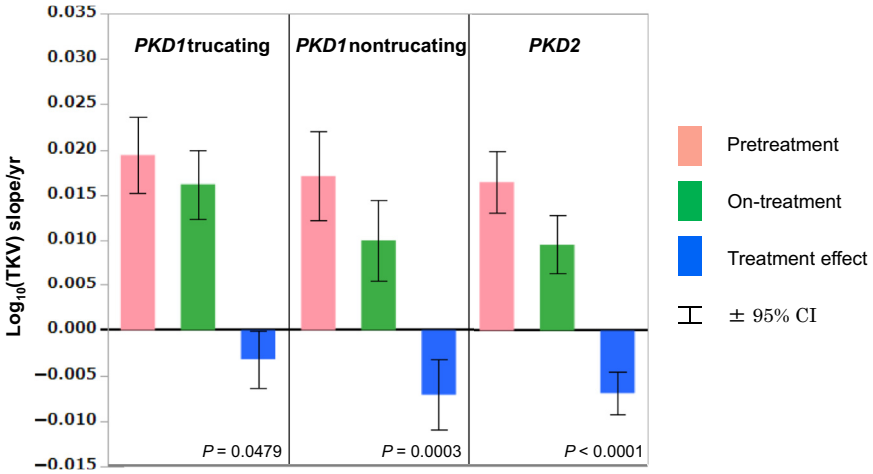

Figure 3. Comparison of change in $\log_{10}$(TKV) slope with tolvaptan treatment according to *PKD* mutation types (Table 4). TKV, total kidney volume.

from baseline to the first year of treatment. As the eGFR was lower in poor responders than in good responders, the subjects with CKD stage 4 were removed from the relationship analysis. As baseline eGFR was still lower in poor responders than in good responders (Supplementary Table S7), the rapid decline in eGFR in poor responders may have been partly influenced by poorer kidney function. Nevertheless, future benefit of the kidney prognosis may be estimated by changes in eHTKV-α calculated using the TKV measured at the first year, irrespective of a lower eGFR.

Table 5. Comparison of 24-hour urine data related to renal osmotic response to tolvaptan between sexes

			Continuous treatment-years				
Variables	Group	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients (male)		118 (53)	111 (51)	98 (47)	87 (39)	69 (30)	38 (16)
Serum osmolality (mOsm/kg)	Total	290.6 ± 3.7	292.8 ± 3.5	293.0 ± 3.6	293.2 ± 3.7	293.1 ± 3.4	293.4 ± 3.5
	P value	–	0.0001	<0.0001	<0.0001	0.0004	<0.0001
	Male	291.7 ± 3.7	293.7 ± 3.6	294.0 ± 3.6	294.0 ± 3.4	294.2 ± 3.5	294.3 ± 3.5
	Female	289.7 ± 3.4	292.0 ± 3.3	292.1 ± 3.4	292.4 ± 3.3	292.9 ± 3.3	292.8 ± 3.5
	*P** value	0.0025	0.0088	0.0083	0.0300	0.1262	0.1811
Serum Na concentration (mEq/l)	Total	140.8 ± 0.3	141.4 ± 0.3	141.4 ± 0.3	141.4 ± 0.3	141.3 ± 0.3	141.4 ± 0.3
	P value	–	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Male	140.7 ± 0.3	141.3 ± 0.3	141.3 ± 0.3	141.3 ± 0.3	141.3 ± 0.3	141.4 ± 0.3
	Female	140.8 ± 0.3	141.4 ± 0.3	141.5 ± 0.3	141.4 ± 0.3	141.4 ± 0.3	141.4 ± 0.3
	*P** value	0.1484	0.2737	0.0297	0.0677	0.1382	0.9847
Urine volume (ml per 1.73 m^2)	Total	2024 ± 160	4003 ± 156	4000 ± 156	3983 ± 153	3966 ± 155	3967 ± 163
	P value	–	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Male	2115 ± 141	4100 ± 136	4084 ± 138	4080 ± 131	4072 ± 128	4081 ± 133
	Female	1950 ± 135	3921 ± 123	3922 ± 129	3904 ± 121	3884 ± 121	3884 ± 132
	*P** value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Urine osmolality (mOsm/kg)	Total	381 ± 14	190 ± 14	190 ± 14	188 ± 14	187 ± 14	188 ± 14
	P value	–	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Male	381 ± 13	191 ± 13	189 ± 13	188 ± 15	187 ± 13	191 ± 15
	Female	381 ± 15	189 ± 14	191 ± 14	189 ± 13	187 ± 14	186 ± 14
	*P** value	0.9750	0.5525	0.4634	0.7468	0.9841	0.3003
Urine-to-serum osmolality ratio	Total	1.31 ± 0.05	0.65 ± 0.05	0.65 ± 0.05	0.64 ± 0.05	0.64 ± 0.05	0.64 ± 0.05
	P value	–	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Male	1.31 ± 0.05	0.64 ± 0.05	0.64 ± 0.05	0.64 ± 0.05	0.63 ± 0.05	0.65 ± 0.05
	Female	1.31 ± 0.06	0.65 ± 0.06	0.65 ± 0.05	0.64 ± 0.05	0.64 ± 0.05	0.63 ± 0.05
	*P** value	0.5952	0.9389	0.2471	0.5013	0.8133	0.4641
Free-water clearance (ml/min per 1.73 m^2)	Total	−0.25 ± 0.14	1.09 ± 0.14	1.09 ± 0.14	1.09 ± 0.15	1.09 ± 0.16	1.08 ± 0.14
	P value	–	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Male	−0.20 ± 0.13	1.15 ± 0.13	1.15 ± 0.13	1.16 ± 0.13	1.16 ± 0.14	1.13 ± 0.14
	Female	−0.30 ± 0.13	1.05 ± 0.14	1.03 ± 0.14	1.03 ± 0.14	1.03 ± 0.15	1.04 ± 0.13
	*P** value	<0.0001	<0.0001	<0.0001	<0.0001	0.0004	0.0638
Change in free-water clearance from baseline (ml/min per 1.73 m^2)	Male	0.15 ± 0.27	1.52 ± 0.26	1.50 ± 0.26	1.50 ± 0.24	1.49 ± 0.26	1.48 ± 0.26
	Female	−0.13 ± 0.25	1.22 ± 0.24	1.21 ± 0.25	1.19 ± 0.25	1.15 ± 0.25	1.16 ± 0.25
	Difference	0.28 ± 0.05	0.30 ± 0.05	0.30 ± 0.05	0.32 ± 0.05	0.34 ± 0.06	0.31 ± 0.08
	*P** value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0006

eGFR, estimated glomerular filtration rate; HSD, honestly significant difference.
Data are the mean ± SD, except for the difference in change in free-water clearance from baseline (mean ± SE). Data are derived from 24-hour urine collection. Differences between baseline and treatment-years were compared by the Turkey-Kramer HSD test, and those between sexes were by analysis of variance adjusting for age, sex, eGFR, and treatment. *P* and *P** values are for comparisons between baseline and 5 treatment-years and between sexes, respectively.

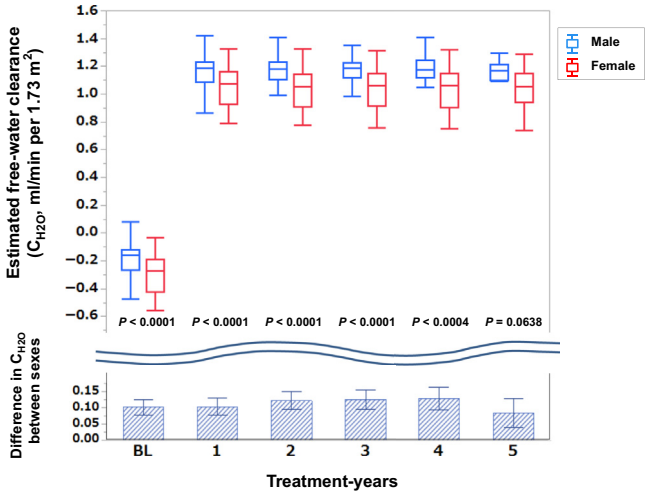

Figure 4. Free-water clearance, adjusted by age, sex, eGFR, and treatment, is illustrated before and after tolvaptan treatment (Table 5). Lines are the median, and boxes indicate 75% and 25% intervals. Bars represent maximum and minimum points. The bars in the lower column indicate the mean difference (±SE) in C_{H2O} between sexes. BL, baseline; eGFR, estimated glomerular filtration rate.

The decrease in the $\log_{10}$(TKV) slope with tolvaptan was larger in subjects with *PKD2* mutation than in those with *PKD1*-truncating type mutation (Table 4). The prognostic value of the PROPKD score was reported using a genotyped subgroup of the TEMPO3/4 trial,[34] but the difference in tolvaptan effects among *PKD* mutation types has not been reported and awaits further study with a larger population.

In subjects with ADPKD, plasma copeptin levels were reported to be higher in males than in females at baseline and increased approximately 3-fold by tolvaptan treatment, with higher levels being maintained in males.[35] Females in the general population have lower plasma vasopressin levels and a higher sensitivity to vasopressin than males.[36–39] The higher sensitivity to vasopressin may correspond to the higher V2R mRNA and protein expression in female Sprague-Dawley rats.[11] The lower serum osmolality, lower urine volume, and lower free-water clearance in females than in males suggested that more free water was reabsorbed in the kidney at both baseline and during the 5-year tolvaptan treatment period in females than in males (Table 5 and Supplementary Figure S3B).

eHTKV-α, used as a complementary analytical method, is a simple and sensitive biomarker to estimate the TKV growth rate. eHTKV-α is relatively stable during the off-treatment period, and its decrease from baseline is used as an estimation of the treatment effects on TKV slope.[13] The treatment effects on the TKV growth rate in the 5-year period were also verified by the changes in eHTKV-α (Supplementary Table S4).

None of the patients discontinued tolvaptan owing to aquaresis-related adverse events. This is significantly different from the 8% discontinuation rate in the TEMPO 3:4 trial.[6] This difference may be due to patients' knowledge of drug effects, no uncertainty on placebo, and management of pollakiuria by reducing the tolvaptan dose. Hepatic injury was observed in 9 patients (7.6%), but it was controllable by the early detection and discontinuation of tolvaptan.

The effects of transient or long-term withdrawal of tolvaptan treatment on TKV and eGFR slopes remained unclear. The consequences of transient interruption were inadvertently observed,[7] but the influences of continued withdrawal of tolvaptan on the TKV and eGFR slopes remain to be investigated.

In conclusion, this study revealed that tolvaptan can attenuate the TKV increase during long-term continued treatment, with greater effects in females. The effects on eGFR were not significant in males likely because of androgen stimulation of cystogenesis, analytical robustness of different eGFR trajectories, small patient number, and influence of the longitudinal-type study. The percent change in eHTKV-α from baseline to the first treatment-year may estimate future benefit of eGFR slope and awaits further study using a large number of patients. The V2R-cAMP-aquaporin axis was activated more in females than in males irrespective of V2R inhibition.

Table 6. Comparison of eGFR change between good and poor responders divided by the extent of decrease in eHTKV-α from baseline to the first treatment-year with tolvaptan in patients with baseline CKD stages 1 to 3

		eGFR (ml/min per 1.73 m^2) during continuous treatment-years				
Groups/category	Baseline eGFR	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients (good responder)	90 (45)	90 (45)	84 (44)	79 (41)	65 (32)	37 (18)
Good responder	57.3 ± 12.2	47.9 ± 11.8	46.8 ± 11.7	46.0 ± 11.7	46.3 ± 11.8	45.9 ± 10.4
Poor responder	52.4 ± 12.2	41.7 ± 11.9	40.5 ± 11.3	38.2 ± 11.6	36.2 ± 12.5	33.3 ± 16.1
Difference ± SE	−5.0 ± 2.6	−6.2 ± 2.5	−6.3 ± 2.5	−7.8 ± 2.6	−10.0 ± 3.0	−12.6 ± 4.5
P value	0.0572	0.0145	0.0141	0.0042	0.0015	0.0080

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; eHTKV-α, estimated height-adjusted total kidney volume growth rate α.
Good responders were defined as subjects with a decrease in eHTKV-α ≥2.94% from baseline to the first treatment-year. Poor responders were those with a decrease in eHTKV-α <2.94% or an increase from baseline to the first treatment-year. The median percent decrease in eHTKV-α from the mean of 3 pretreatment-years to the first treatment-year with tolvaptan in patients with CKD stages 1 to 3 was 2.94%. Subjects with baseline CKD stage 4 were excluded owing to the preponderance of CKD stage 4 in poor responders. The estimated glomerular filtration rate, eGFR, was calculated using the modified IDMS–MDRD Study equation with the Japanese coefficient 0.808 and adjusted by sex, age, TKV, and treatment. Data are the mean ± SD except for the difference between 2 groups. *P* values were calculated using analysis of variance.

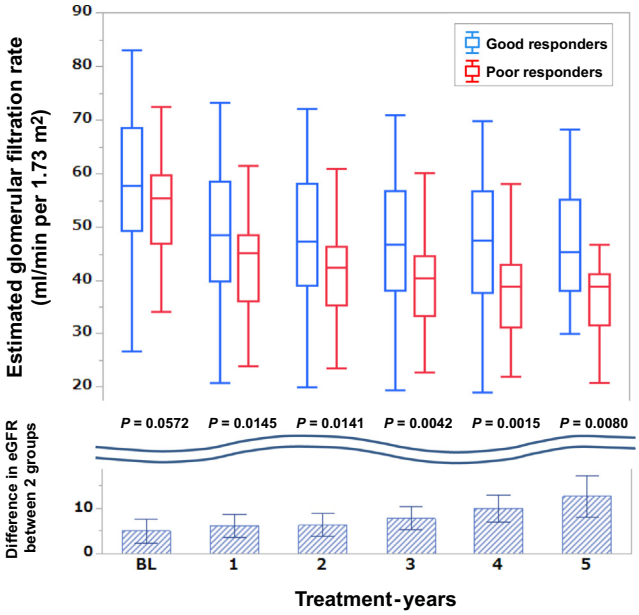

Figure 5. Comparison of changes in eGFR between good and poor responders with CKD stage 1 to 3. Classification of good and poor responders is explained in Table 6 and the text. Lines in the box are the median, and boxes indicate 75% and 25% intervals. Bars represent maximum and minimum points. The bars in the lower column indicate the mean difference (±SE) in eGFR between good and poor responders. BL, baseline; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

DISCLOSURE

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DATA AVAILABILITY STATEMENT

Data are available from the authors on reasonable request and with permission from the Ethics Committee of Kyorin University School of Medicine and Ethics Committee of the National Center of Neurology and Psychiatry.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Estimation of sample size.

Table S2. Comparison of demographic characteristics between males and females.

Table S3. Changes in slopes of $\log_{10}$(TKV) and eGFR with treatment analyzed without adjustment by covariates.

Table S4. Changes in eHTKV-α from baseline to treatment year with tolvaptan.

Table S5. Distribution of pathogenic *PKD1* and *PKD2* mutations.

Table S6. Comparison of 24-hour urine data between baseline and treatment-year and between sexes.

Table S7. Comparison of baseline demographic characteristics between good and poor responders in patients with CKD stage 1 to 3.

Table S8. Main adverse events.

Figure S1. The individual trajectories of $\log_{10}$(TKV) (A) and eGFR (B) against pre- and on-treatment years.

Figure S2. The observed-year-specific curves of $\log_{10}$(TKV) (A) and eGFR (B) analyzed using the generalized additive model (GAM).

Figure S3. (A) Putative mechanisms of sex differences in V2R-cAMP-PKA-mediated cystogenesis in ADPKD cyst-lining cells. (B) Putative mechanisms of sex differences in V2R-cAMP-PKA-mediated renal osmotic response in CD cells in ADPKD.

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