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 m². 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 log10(TKV) slope/yr decreased from the pretreatment period (P < 0.0001) and the estimated height-adjusted TKV growth rate (eHTKV-a, %/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-a from baseline to the first treatment-year than 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-a 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.

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

The vasopressin-cAMP-osmolality axis is abnormal in ADPKD. Patients with ADPKD exhibited a significant defect both in the release of vasopressin and in the V2R-mediated renal osmotic response. The expression of V2R mRNA, its protein, and aquaporin 2 was higher in female non-PKD rats than in male non-PKD rats. 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-\( \alpha \) from baseline and changes in eGFR 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\( \text{TKV} \). 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 \( \geq 750 \text{ ml} \), TKV growth rate \( \geq 5\% / \text{yr} \), and eGFR \( \geq 15 \text{ ml/min per 1.73 m}^2 \). 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, and subjects with an average TKV growth rate \(< 5\%/\text{yr} \) 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. Patients with interrupted tolvaptan intake for \( > 1 \text{ month} \) were excluded from the study.

We calculated 100 patients to be necessary assuming a log\( 10(\text{TKV}) \) 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 \(< 50 \text{ kg} \) or aged \( \geq 65 \text{ years} \), 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.

TKV was measured using a standard protocol for magnetic resonance imaging without contrast medium. As a cohort study, TKV and 24-hour urine were measured basically once a year, 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 (\( \pm 1 \text{ month} \) ) or before withdrawal (\( \pm 2 \text{ month} \) ) 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. Protein intake was estimated using 24-hour urine data by Maroni’s equation.

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

**Estimated HTKV Growth Rate $\alpha$**

The eHTKV-$\alpha$ originates from the Mayo Class and was calculated by the following equation: $\text{HTKV}_t = K \left(1 + \frac{\text{eHTKV}-\alpha}{100}\right)^t$, where HTKV$_t$ 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-$\alpha$. The decrease in eHTKV-$\alpha$ from baseline implies treatment effects on the HTKV growth rate and was used for prespecified and additional analytical methods.

**Statistical Methods**

Normally distributed variables were expressed as mean $\pm$ SD or SE. Differences between groups were tested using the $\chi^2$ 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 $\log_{10}(\text{TKV})$ 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-$\alpha$ from baseline to treatment-years were compared...
Table 1. Baseline demographic and clinical characteristics of patients according to treatment-years

| Characteristics | Enrolled (total) | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | P value |
|----------------|-----------------|--------|--------|--------|--------|--------|---------|
| 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 (2.4–3.8) | 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 ± 2.9 | 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 (3.0–4.12) | 1 (0.91–0.96) | 2 (1.92–1.98) | 3 (2.93–2.98) | 4 (3.9–3.9) | 5 (4.9–5.0) |         |
| Treatment-years | 3.6 ± 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 CKD stage, n (%) |         |         |         |         |         |         |         |
| Stage 1 | 1 (eGFR ≥60) | 34 (28.8) | 33 (29.7) | 31 (31.3) | 30 (34.1) | 27 (37.5) | 16 (42.1) | 0.4791 |
| Stage 2 | 3 (eGFR 45–59) | 23 (19.5) | 23 (20.7) | 23 (23.2) | 20 (22.7) | 16 (22.2) | 7 (18.4) |         |
| Stage 3 | 3 (eGFR 30–44) | 33 (28.0) | 30 (27.0) | 26 (26.3) | 25 (28.4) | 20 (27.8) | 14 (36.8) |         |
| Stage 4 | 4 (eGFR 15–29) | 28 (23.7) | 25 (22.5) | 19 (19.2) | 13 (14.8) | 9 (12.5) | 1 (2.6) |         |
| Baseline TKV (ml) | 2153 ± 943 | 2173 ± 951 | 2146 ± 966 | 2092 ± 891 | 2117 ± 890 | 1993 ± 962 | 0.8750 |
| Baseline HTKm (ml/m) | 1305 ± 556 | 1319 ± 561 | 1302 ± 568 | 1274 ± 534 | 1292 ± 537 | 1209 ± 574 | 0.8686 |
| Baseline eHTKV-a (%) | 4.64 ± 1.43 | 4.68 ± 1.45 | 4.71 ± 1.50 | 4.76 ± 1.51 | 4.84 ± 1.56 | 4.81 ± 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 | 0.8907 |
| 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 | 128.9 ± 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 | 37 (31.4) | 34 (30.6) | 34 (34.3) | 31 (35.2) | 25 (34.7) | 15 (39.5) |         |
| PKD2 | 14 (11.9) | 14 (12.6) | 11 (11.1) | 11 (12.5) | 8 (11.1) | 3 (7.9) |         |
| Mutation unidentified or no test | 14 (11.9) | 12 (10.8) | 8 (8.1) | 6 (6.6) | 5 (6.9) | 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 of 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 of 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-a, estimated height-adjusted total kidney volume growth rate a; HTKV, height-adjusted total kidney volume; HTN, hypertension; TKV, total kidney volume.
eHTKV-a calculated by the eHTKV-a equation.1 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 χ² 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 m², 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-a 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 log10(TKV) and eGFR were plotted against pre- and on-treatment-years (Supplementary Figure S1A and B). Age and sex were
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 were not different between the analyses with and without adjustment by sex and age. 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).

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 \((P < 0.0001; \text{ Table 2})\).

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 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\(^a\)       |     |              |         |             |          |             |          |

| 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 | –3.07 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\(^a\)       |     |              |         |             |          |             |          |

\(^a\)Compares difference of treatment effect in the slope of log_{10}(TKV) and eGFR between sexes.
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, the quantitative extent of TKV change with tolvaptan was estimated by the percent change in eHTKV-α from baseline. 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).

Table 3. The estimation of treatment effects of tolvaptan on mean log10(TKV) for each year

| Bl, baseline; TKV, total kidney volume; Tx, treatment. The pretreatment mean log10 (TV) was estimated by a regression line analyzed using pretreatment data (B). The on-treatment mean log10 (TV) was estimated using pre- and on-treatment data (A). The on-treatment mean log10 (TV) was calculated by (B) and A, and at each of the estimated means, TV was converted from log10 (TV). |
|**Change in TKV from previous year** | **P value** |
|**On-Tx** | **Pre-Tx** | **On-Tx** | **Pre-Tx** |
|**Pre- and on-Tx year** | **Estimated mean (A)** | **95% CI** | **SE** | **Estimated mean (B)** | **95% CI** | **SE** |
| 1 | 3.176 | 3.110–3.243 | 0.004 | 2032 | 0.004 | 2022 |
| 2 | 3.195 | 3.127–3.263 | 0.004 | 2043 | 0.004 | 2032 |
| 3 | 3.215 | 3.145–3.285 | 0.004 | 2052 | 0.004 | 2043 |
| 4 | 3.235 | 3.165–3.305 | 0.004 | 2062 | 0.004 | 2052 |
| 5 | 3.255 | 3.185–3.325 | 0.004 | 2072 | 0.004 | 2062 |
| 6 | 3.275 | 3.205–3.345 | 0.004 | 2082 | 0.004 | 2072 |
| 7 | 3.295 | 3.225–3.365 | 0.004 | 2092 | 0.004 | 2082 |
| 8 | 3.315 | 3.245–3.385 | 0.004 | 2102 | 0.004 | 2092 |
| 9 | 3.335 | 3.265–3.405 | 0.004 | 2112 | 0.004 | 2102 |
| 10 | 3.355 | 3.285–3.425 | 0.004 | 2122 | 0.004 | 2112 |

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 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. The acute TKV decrease at 1 to 3 weeks observed in short-term tolvaptan studies is consistent with this decrease. The significant decrease in log10(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 fluid.
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The estimated pretreatment means were extrapolated to both pretreatment and on-treatment periods. Range is the 95% upper and lower CIs. BL, baseline; TKV, total kidney volume.

The slope of TKV was analyzed by a linear mixed-effect model by fixing TKV to log10(TKV) with fixed effects of age, sex, mutation type, whole TKV measurement year and year during tolvaptan treatment.

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 cells25 and dihydrotestosterone stimulation of signaling pathways downstream of V2R-stimulated cAMP and protein kinase A production, as observed in PKD animal models26,27 (Supplementary Figure S3A). The effects of tolvaptan to suppress the TKV growth rate, estimated 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 \( \log_{10}(\text{TKV}) \) 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 and change in log10(TKV).

### Table 4. Comparison of baseline eHTKV-α and change in log10(TKV) slope with tolvaptan treatment according to PKD mutation types

| Mutation types | N | Mean ± SE | 95% CI | Mean ± SE | 95% CI | Mean ± SE | 95% CI | Mean ± SE | 95% CI | P value |
|----------------|---|-----------|--------|-----------|--------|-----------|--------|-----------|--------|--------|
| **Baseline eHTKV-α** | | | | | | | | | | |
| 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 |
| **Slope of log10(TKV)/yr** | | | | | | | | | | |
| 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 \( \log_{10}(\text{TKV}) \) 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 \( \log_{10}(\text{TKV}) \) slope between pre- and on-treatment.
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-2 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

| Variables                         | Continuous treatment-years |                |                |                |                |
|-----------------------------------|-----------------------------|----------------|----------------|----------------|----------------|
|                                   |                             | Number of patients (male) | 118 (53) | 111 (51) | 98 (47) | 87 (39) | 69 (30) | 38 (16) |
|                                   |                             | Serum osmolality (mOsm/kg) | 290.6 ± 3.7 | 292.8 ± 3.5 | 293.0 ± 3.6 | 293.2 ± 3.7 | 291.1 ± 3.4 | 293.4 ± 3.5 |
|                                   |                             | P value                      | 0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0004 | <0.0001 |
|                                   |                             | Serum Na concentration (mEq/l) | 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                      | 0.0025 | 0.0068 | 0.0000 | 0.0000 | 0.1262 | 0.1811 |
|                                   |                             | Urine volume (ml per 1.73 m²) | 2024 ± 160 | 4003 ± 156 | 4000 ± 156 | 3983 ± 153 | 3966 ± 155 | 3967 ± 163 |
|                                   |                             | P value                      | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|                                   |                             | Urine Na concentration (mEq/l) | 381 ± 14 | 190 ± 14 | 190 ± 14 | 188 ± 14 | 187 ± 14 | 188 ± 14 |
|                                   |                             | P value                      | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|                                   |                             | Urine-osmolality ratio (mOsm/kg) | 381 ± 14 | 190 ± 14 | 190 ± 14 | 188 ± 14 | 187 ± 14 | 188 ± 14 |
|                                   |                             | P value                      | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|                                   |                             | Free-water clearance (ml/min per 1.73 m²) | 0.25 ± 0.14 | 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 | <0.0001 |
|                                   |                             | Change in free-water clearance from baseline (ml/min per 1.73 m²) | 0.15 ± 0.27 | 1.50 ± 0.26 | 1.50 ± 0.26 | 1.50 ± 0.24 | 1.49 ± 0.26 | 1.48 ± 0.26 |
|                                   |                             | P value                      | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

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.
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-\(\alpha\), used as a complementary analytical method, is a simple and sensitive biomarker to estimate the TKV growth rate. eHTKV-\(\alpha\) 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-\(\alpha\) (Supplementary Table S4).

None of the patients discontinued tolvaptan owing to aquareasis-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-\(\alpha\) 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-\(\alpha\) from baseline to the first treatment-year with tolvaptan in patients with baseline CKD stages 1 to 3

| Groups/culture | 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 | 0.0008 |

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; eHTKV-\(\alpha\), estimated height-adjusted total kidney volume growth rate \(\alpha\).

Good responders were defined as subjects with a decrease in eHTKV-\(\alpha\) ≥2.94% from baseline to the first treatment-year. Poor responders were those with a decrease in eHTKV-\(\alpha\) < 2.94% or an increase from baseline to the first treatment-year. The median percent decrease in eHTKV-\(\alpha\) 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–MR4D 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.
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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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