Dose-Dependent Effect of Tolvaptan on Renal Prognosis in Patients with Autosomal Dominant Polycystic Kidney Disease

Taro Akihisa,1 Shun Manabe,1 Hiroshi Kataoka,1 Shiho Makabe,1 Rie Yoshida,1 Yusuke Ushio,1 Kentaro Watanabe,1 Masayo Sato,1 Ken Tsuchiya,2 Toshio Mochizuki,1 and Kosaku Nitta1

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Key Points
- This is the first report to describe dose dependency in the effects of tolvaptan treatment for autosomal dominant polycystic kidney disease.
- The weight-adjusted average daily dose of tolvaptan was found to be a factor that significantly affected the change in eGFR.
- If a patient shows tolerance, increasing the tolvaptan dose to the maximum should be considered.

Introduction
Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, in which multiple renal cysts develop and renal dysfunction progresses. Approximately half of patients with ADPKD reach ESKD by 60 years of age.

The clinical studies on tolvaptan treatment for ADPKD, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial, and the Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial showed that tolvaptan suppressed both the increase in kidney volume and the reduction in renal function (1,2). In these studies, a starting dose of 60 mg was increased to 90–120 mg, if tolerated, during the 3-week titration period. In phase 2 of the TEMPO 3:4 study, tolvaptan was reported to induce a dose-dependent reduction in urinary osmolality, which was maintained over a longer duration, and an increase in urine volume (3,4). A study using cultured human ADPKD cells demonstrated that tolvaptan suppressed the production of cAMP—which is related to cyst formation, cell proliferation, and in vitro cyst growth—in a dose-dependent manner (5). In a study using animal models of cystic kidney disease, tolvaptan not only increased the urine volume and reduced the urinary osmolality, but it also inhibited the increase in kidney volume and reduced renal cAMP levels in a dose-dependent manner (6). However, no studies have investigated the dose-dependent effects of tolvaptan in patients with ADPKD. Therefore, we aimed to verify the dose-dependent inhibitory effects of tolvaptan on the reduction in renal function in patients with ADPKD.

Materials and Methods
Protocol
The brief protocol of this study was as follows: (1) the goal was to clarify whether the integrated weight-adjusted average daily dose of tolvaptan affected renal prognosis in a dose-dependent manner among patients with ADPKD; (2) we included patients with ADPKD who had >750 ml in total kidney volume (TKV) and >5% in annualized TKV growth rate, but patients with an eGFR of <15 ml/min per 1.73 m² were contraindicated; (3) we excluded patients with observation periods of <6 months, and patients who had missing TKV data in three dimensional (3D) reconstruction–computed tomography images; and (4) we assessed the annual percentage change in eGFR as a defined outcome. The main variable was the weight-adjusted average daily dose of tolvaptan.

Patients
We enrolled 92 patients with ADPKD who were administered tolvaptan at Tokyo Women’s Medical University hospital between September 2014 and February 2019. A flow chart of the study population is shown in Figure 1. We excluded eight patients whose cumulative period of tolvaptan was <6 months. Six patients discontinued tolvaptan; two patients discontinued due to liver enzyme elevation, two due to decreased renal function (eGFR of <15 ml/min per 1.73 m²), and two due to the onset of other diseases. One patient died from subarachnoid hemorrhage, and one transferred to another hospital. We also excluded five patients who had missing TKV data in 3D reconstruction–computed tomography images. Finally, 79 patients were eligible for this study.

All procedures performed were in accordance with the ethical standards of the institutional research committee.
Study Design
This was a single-center, prospective, observational cohort study. Tolvaptan was initiated on admission for 3 days. The starting dose was 60 mg, which was administered as a 45 mg dose after breakfast and a 15 mg dose after dinner for patients with a creatinine clearance rate of $\geq 30$ ml/min per 1.73 m$^2$. The initial tolvaptan dose was reduced in patients with a creatinine clearance rate of $<30$ ml/min per 1.73 m$^2$. After discharge, patients visited the outpatient department monthly for follow-up. The tolvaptan dosage was gradually increased to 120 mg/d, depending on tolerability, according to the Japanese package insert. Tolvaptan was discontinued when the eGFR fell $<15$ ml/min per 1.73 m$^2$, according to the Japanese package insert, and follow-up of the patient was terminated. If tolvaptan was discontinued and then resumed, the cumulative administration period was calculated. During follow-up, 16 patients had a long withdrawal period, with an average of 0.42 years.

Covariate Assessments
Blood and urine were sampled immediately before oral administration of tolvaptan. TKV was measured within 3 months before starting tolvaptan, using the 3D workstation of Ziosation2 version 2.4.2.3 (Ziosoft, Inc., Tokyo, Japan). Our defined outcome for assessment was the annual percentage change in eGFR. To calculate the annual percentage change in eGFR, the annual percentage change was calculated as follows:

$$\frac{\text{eGFR at the end of follow-up duration} - \text{eGFR at baseline}}{\text{eGFR at baseline}} \times 100\%$$

Table 1. Patient characteristics ($n=79$)

| Variables                                    | Value ($n=79$) |
|----------------------------------------------|----------------|
| **Clinical findings**                        |                |
| Age (yr), mean±SD                            | 42.9±9.7       |
| Sex (men), n (%)                             | 44 (56)        |
| Body weight (kg), mean±SD                    | 66.5±12.9      |
| Body mass index (kg/m$^2$), mean±SD          | 23.4±3.5       |
| Follow-up duration (yr), mean±SD             | 2.52±1.48      |
| Initial tolvaptan dose (mg/d), mean±SD       | 56.9±9.6       |
| Tolvaptan dose at the end of follow-up duration (mg/d), mean±SD | 84.1±40.6 |
| Weight-adjusted average daily dose of tolvaptan (mg/kg per d), mean±SD | 1.14±0.58 |
| **Laboratory findings**                      |                |
| Hemoglobin (g/dl), mean±SD                   | 13.3±1.5       |
| Serum albumin (g/dl), mean±SD                | 4.40±0.26      |
| Serum creatinine (mg/dl), mean±SD            | 1.34±0.65      |
| eGFR (ml/min per 1.73 m$^2$), mean±SD        | 68.6±4.3       |
| Urine protein (g/gCre), median (IQR)          | 0.11 (0.06–0.3) |
| Urine osmolality at baseline (mOsm/L), mean±SD| 358±138        |
| Urine osmolality after final titration of tolvaptan (mOsm/L), mean±SD | 179±74 |
| Urine osmolality at the end of follow-up duration (mOsm/L), mean±SD | 186±89 |
| htTKV (ml/m), mean±SD                        | 1217±679       |
| **Comorbidities, n (%)**                     |                |
| Hypertension$^a$                             | 62 (78)        |
| Hyperuricemia$^b$                            | 34 (43)        |
| Hypertriglyceridemia$^c$                     | 23 (29)        |
| Low HDL cholesterol$^d$                      | 11 (14)        |
| High LDL cholesterol$^e$                     | 21 (27)        |

$^a$Hypertension was defined as a systolic BP of $\geq 140$ mm Hg, diastolic BP of $\geq 90$ mm Hg, or the need for an antihypertensive agent.

$^b$Hyperuricemia was defined as a serum uric acid level of $\geq 7.0$ mg/dl or the need for an antihyperuricemic agent.

$^c$Hypertriglyceridemia was defined as a serum triglyceride level of $\geq 150$ mg/dl or the need for an antidyyslipidemic agent.

$^d$Low HDL cholesterol was defined as a serum HDL cholesterol level of $\leq 40$ mg/dl in men and $\leq 50$ mg/dl in women or the need for an antidyyslipidemic agent.

$^e$High LDL cholesterol was defined as a serum LDL cholesterol level of $\geq 140$ mg/dl or the need for an antidyyslipidemic agent.
positively correlated (β=0.31, P=0.005).

change in eGFR, eGFR values from 1 month after the start of tolvaptan to the final follow-up were used. The regression line was calculated from these values, and the rate of eGFR change was calculated.

To assess our variables of interest, the average daily dose of tolvaptan was calculated by dividing the actual prescribed dose by the actual administration period as follows: (actual prescribed dose)/(total follow-up day−withdrawal day). Therefore, the average daily dose of tolvaptan is reduced in patients with a longer tolvaptan withdrawal period. Using the body weight measurement that was recorded at the time of admission at the start of tolvaptan administration, we calculated the weight-adjusted average daily dose of tolvaptan. To calculate height-adjusted TKV (htTKV), TKV was divided by the height recorded at admission at the start of tolvaptan administration.

Statistical Analysis
Categoric variables are reported as numbers and percentages, unless otherwise stated. Data were evaluated using the chi-squared test, t test, Mann–Whitney U test, or one-way ANOVA. The Pearson correlation coefficient was used to determine the bivariate relationship between the weight-adjusted average daily dose of tolvaptan (mg/kg per day) and the annual percentage change in eGFR (percentage per year). Univariate and multivariate linear regression analyses were performed to investigate factors related to the percentage change in eGFR. Factors with a P value <0.1 in the univariate analysis were included in the multivariate analysis, as were general factors, such as sex, age, and eGFR. The sample size calculation was determined on the basis of the assumption that a minimum of five subjects were required for regression analysis (7,8). JMP Pro version 14.1.0 (SAS Institute, Cary, NC) was used for statistical analysis. P<0.05 was considered statistically significant.

Results
The patient characteristics are presented in Table 1. The baseline eGFR was 53.2±24.5 ml/min per 1.73 m². The average initial dosage of tolvaptan was 56.9 mg/d, and the weight-adjusted average daily dosage of tolvaptan was 1.14 mg/kg per day. The mean follow-up duration was 2.52 years. Although three patients showed large decline in eGFR (Supplemental Figure 1), no AKI occurred in any patient during the follow-up period. The bivariate analysis indicated that the weight-adjusted average daily dose of tolvaptan was significantly and positively correlated with the percentage change in eGFR (β=0.31, P=0.005; Figure 2). In the univariate analysis, the weight-adjusted average daily dose of tolvaptan (β=0.31, P=0.005), hemoglobin (β=0.22, P=0.05), eGFR (β=0.35, P=0.002), urine protein (β=−0.43, P<0.001), and htTKV (β=−0.36, P=0.0009) were significantly associated with the percentage change in eGFR (Table 2). In the multivariate analysis, the weight-adjusted average daily dose of tolvaptan (β=0.22, P=0.03), hemoglobin (β=0.28, P=0.02), eGFR (β=0.31, P=0.02), and urine protein (β=−0.31, P=0.002) were again identified as significant independent predictors (Table 2). However, htTKV was not identified as a significant independent predictor in the multivariate analysis (β=−0.02, P=0.87; Table 2).

Discussion
This study aimed to determine whether the integrated weight-adjusted average daily dose of tolvaptan affected
the renal prognosis in a dose-dependent manner among patients with ADPKD. In this study, although the doses were increased to 120 mg according to tolerability, the patients sometimes reduced or stopped medication due to aquaretic-related symptoms (9). Thus, the integrated dose derived from the actual prescription quantity was used, and the weight-adjusted doses were calculated as the index. In the TEMPO 3:4 study, the mean dosage of tolvaptan was 99 mg/d in the entire population, but was 95 mg/d in the Japanese subpopulation (10). However, the inhibitory effects on both the increase in TKV and the reduction in eGFR were stronger in the Japanese subpopulation than that in the entire population (1,10). Because the mean body weight was 79.47 kg in the entire population, and 64.94 kg in the Japanese subpopulation, the mean weight-adjusted doses were 1.25 mg/kg per day and 1.46 mg/kg per day, respectively. Although differences by ethnicity should also be considered, these findings suggest that the efficacy of tolvaptan is influenced by weight-adjusted doses.

In conclusion, the weight-adjusted average daily dose of tolvaptan was found to be a factor that significantly affected the change in eGFR. Hence, if there is tolerance, increasing the tolvaptan dose to the maximum should be considered.

Disclosures

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Author Contributions

T. Akihisa, H. Kataoka, and S. Manabe were responsible for formal analysis and validation; T. Akihisa, H. Kataoka, and T. Mochizuki were responsible for methodology; T. Akihisa, S. Makabe, M. Sato, Y. Ushio, K. Watanabe, and R. Yoshida were responsible for data curation; T. Akihisa and S. Manabe were responsible for visualization; T. Akihisa, S. Manabe, and T. Mochizuki wrote the original draft; T. Akihisa and T. Mochizuki were responsible for funding acquisition; H. Kataoka, S. Manabe, and T. Mochizuki conceptualized the study, were responsible for investigation, and reviewed and edited the manuscript; S. Manabe was responsible for project administration; T. Mochizuki and K. Tsuchiya were responsible for resources; and K. Nitta and K. Tsuchiya provided supervision.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0017342020/ - DC Supplemental.

Supplemental Figure 1. The changes of eGFR and SCr in three patients who showed large decline in eGFR.

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