Genetics May Predict Effectiveness of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease

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Keywords

Autosomal dominant polycystic kidney disease · Genotype · Polycystic kidney disease 1 · Polycystic kidney disease 2 · Tolvaptan

Abstract

Background: Tolvaptan is the only therapeutic drug for autosomal dominant polycystic kidney disease (ADPKD). The influence of mutations in polycystic kidney disease 1 and 2 genes (*PKD1* and *PKD2*) on the treatment effects of tolvaptan is not well documented in the literature. **Methods:** We retrospectively evaluated the relationship between genotype and the efficacy of tolvaptan in 18 patients with ADPKD who had been treated at Toranomon Hospital and undergone genetic testing between April 2016 and February 2020. **Results:** The annual change in estimated glomerular filtration rate (Δ eGFR/y) from before to after tolvaptan was from a median of -5.5 to -2.5 mL/min/1.73 m² in the *PKD1* truncating group, -3.3 to -2.4 mL/min/1.73 m² in the *PKD1* non-truncating group, -3.1 to -1.6 mL/min/1.73 m² in the *PKD2* group, and -1.9 to -2.6 mL/min/1.73 m² in the group with

no *PKD1/2* mutation. The median degrees of improvement of Δ eGFR/y were 2.5 (45%), 0.4 (10%), 0.6 (28%), and -0.7 (-37%) mL/min/1.73 m², respectively. Compared with the group of patients with any *PKD1/2* mutation, the group with no *PKD1/2* mutation showed significantly less improvement in Δ eGFR/y with tolvaptan (0.6 vs. -0.7 mL/min/1.73 m², respectively; $p = 0.01$) and significantly less improvement in the annual rate of increase in total kidney volume (TKV) with tolvaptan (-6.7 vs. -1.1% , respectively; $p = 0.02$). **Conclusion:** Patients with ADPKD and no *PKD1/2* mutation showed less improvement in Δ eGFR/y and the annual rate of increase in TKV with tolvaptan. Detecting *PKD1/2* mutations may be useful for predicting the effectiveness of tolvaptan.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary cystic kidney disease, affecting 1 in 1,000–2,500 people worldwide [1]. ADPKD has been linked to mutations in 2 genes: polycys-

tic kidney disease 1 (*PKD1*) gene (chromosome 16; 16p13.3) and polycystic kidney disease 2 (*PKD2*) gene (chromosome 4; 4q21); the former mutation was found in 78% of patients and the latter, in 15% [1]. Approximately 7% of patients with ADPKD appear not to have a *PKD1/2* mutation [2, 3]. Among ADPKD patients, the severity of the effects of these mutations on renal survival was reported to be as follows: *PKD1* truncating mutation > *PKD1* non-truncating mutation > *PKD2* mutation > no *PKD1* or *PKD2* mutation [4, 5].

The only therapeutic drug for patients with ADPKD is tolvaptan, a vasopressin V2-receptor antagonist that slows the rate of decline of the estimated glomerular filtration rate (eGFR). The efficacy of tolvaptan was investigated in the randomized, double-blind, placebo-controlled, multicenter, phase 3 TEMPO 3:4 trial [6] and its long-term extension, TEMPO 4:4 [7], and the efficacy in patients with later-stage ADPKD was investigated in the randomized, double-blind, placebo-controlled, multicenter, phase 3 REPRISE trial [8]. A post hoc analysis of TEMPO 4:4 data found statistically significant treatment effects of tolvaptan in the *PKD1* truncating group [7]. However, the treatment effects of tolvaptan in the other groups (*PKD1* non-truncating, *PKD2*, and no *PKD1/2* mutation) and the change in clinical course before and after tolvaptan therapy in each group were unclear. Therefore, in the present study, we evaluated the relation between genetic characteristics and treatment effects of tolvaptan by analyzing clinical variables in patients with ADPKD before and after tolvaptan therapy. To our knowledge, this is the first report of the evaluation of the effectiveness of tolvaptan in patients with ADPKD who do not have a *PKD1/2* mutation.

Materials and Methods

Patients

This study included 21 patients with ADPKD who had been treated with tolvaptan at Toranomon Hospital and undergone genetic testing between April 2016 and February 2020. We previously reported on 14 of these patients [9]. Eligibility requirements included a diagnosis of ADPKD according to the protocol of REPRISE trial modified Pei-Ravine criteria [10–12], with an eGFR >15 mL/min/1.73 m², a total kidney volume (TKV) ≥750 mL, and a TKV growth rate of 5% per year or more. All patients were started on 60 mg of tolvaptan in a split-dose regimen (45 mg in the morning and 15 mg in the evening). The dose was modified according to patients' tolerance; the maximum dose was 120 mg/day.

As an indicator of the decline of renal function, we obtained the eGFR 3–12 times at intervals of a few months (including 1 interval of at least 6 months) both before and after treatment with tolvaptan. The eGFR was calculated with the Japanese eGFR equation

[13]. Then, we used the eGFR data to draw an approximate curve and estimated the decline in renal function from the slope of the curve ($\Delta\text{eGFR}/\text{y}$) for each patient before and after treatment with tolvaptan. As an indicator of the percentage increase in TKV ($\%\Delta\text{TKV}/\text{y}$), we assessed TKV twice before treatment with tolvaptan (at least 6 months between measurements; median time between measurements: 2 years) and twice after starting treatment with tolvaptan (almost 1.5–3 years between measurements; median time between measurements: 2.3 years). TKV was calculated from CT scans or MR images by the modified ellipse method with the following formula: volume = $\pi/6 \times \text{length} \times \text{width} \times \text{depth}$ [14].

Most of the patients were seen at our hospital at least 3 times before and after treatment with tolvaptan, and we were able to collect the required data. However, we were not able to confirm the diachronic data on renal function before tolvaptan therapy in 3 patients and, therefore, excluded them from the study. This study was performed in accordance with the Declaration of Helsinki and was approved by the research Ethics Committees of Toranomon Hospital and Tokyo Medical and Dental University Hospital. Written informed consent was obtained from all patients.

Genetic Analysis

Genetic analysis was performed with capture-based next-generation sequencing according to the method reported previously [9, 15, 16]. The next-generation sequencing panel provided good coverage of the exonic regions of both *PKD1* and *PKD2*, except for exon 1 of *PKD1*. This approach detected no mutations of 6 pseudogenes.

Statistical Analysis

We analyzed the data of the 18 patients with ADPKD and tabulated the clinical characteristics by the type of mutation. Categorical variables were summarized as the number (percentage) and continuous variables as the mean with the standard deviation or median with the interquartile range (IQR). The association between genotype (4 groups: *PKD1* truncating, *PKD1* non-truncating, *PKD2*, and no *PKD1/2*) and the clinical data was analyzed by the Kruskal-Wallis test; and the association between each of the 4 groups (*PKD1* truncating vs. *PKD1* non-truncating, *PKD1* truncating vs. *PKD2*, *PKD1* truncating vs. no *PKD1/2*, *PKD1* non-truncating vs. *PKD2*, *PKD1* non-truncating vs. no *PKD1/2*, and *PKD2* vs. no *PKD1/2*) or the existence of a *PKD1/2* mutation and the change in $\Delta\text{eGFR}/\text{y}$ or $\%\Delta\text{TKV}/\text{y}$ before and after tolvaptan therapy were analyzed by the Wilcoxon rank-sum (Mann-Whitney *U*) test. For all analyses, $p < 0.05$ was taken to indicate statistical significance. Analyses were conducted with STATA® SE version 14.0 (StataCorp, College Station, TX, USA).

Results

Genetic, Clinical, and Laboratory Characteristics

On the basis of the probable genetic cause of ADPKD, the 18 patients were classified into the following 4 groups: *PKD1* truncating group (4 patients), *PKD1* non-truncating group (7 patients), *PKD2* group (4 patients), and no *PKD1/2* group (3 patients). Data on the clinical and laboratory characteristics of these groups at the start of tolvap-

Table 1. Summary of clinical and laboratory characteristics

	<i>PKD1</i> truncating, <i>n</i> = 4	<i>PKD1</i> non-truncating, <i>n</i> = 7	<i>PKD2</i> , <i>n</i> = 4	No <i>PKD1/2</i> , <i>n</i> = 3
Age, years	52 [52–55]	49 [45–57]	46 [44–49]	53 [50–54]
Male, <i>n</i> (%)	1 (25)	4 (57)	3 (75)	0 (0)
Female, <i>n</i> (%)	3 (75)	3 (43)	1 (25)	3 (100)
Family history, <i>n</i> (%)	1 (25)	2 (29)	1 (25)	0 (0)
BMI	24.0 [21.0–26.5]	23.0 [21.0–24.5]	22.5 [20.8–24.3]	26.0 [24.5–26.0]
MAP	101 [95–105]	91 [87–97]	96 [87–107]	91 [90–93]
Antihypertensive drug use, <i>n</i> (%)	4 (100)	6 (86)	3 (75)	2 (67)
eGFR	28.0 [23.7–35.6]	39.1 [34.8–56.9]	65.0 [58.6–76.0]	54.5 [54.0–57.6]
Height-adjusted TKV, mL/m	1,619 [1,191–2,318]	901 [728–1,592]	707 [521–900]	955 [758–998]
Number of cysts in the middle section of the left kidney	39 [36–42]	25 [23–36]	25 [23–31]	23 [22–25]
Diameter of the largest cyst, mm	72.0 [66.4–73.4]	49.7 [44.6–79.6]	64.3 [59.9–69.4]	73.1 [67.2–73.6]
>20 liver cysts, <i>n</i> (%)	4 (100)	3 (43)	4 (100)	2 (67)
Intracranial aneurysm, <i>n</i> (%)	1 (25)	2 (29)	0 (0)	1 (33)
Follow-up, years [after tolvaptan]	3.8 [2.6–4.5]	4.5 [3.5–5]	2.8 [2.4–3.1]	2.5 [2–2.8]
Average dose of tolvaptan, mg	54	77	60	60

Data are expressed as number (percentage) or median [25th–75th percentiles]. eGFR, estimated glomerular filtration rate; PKD, polycystic kidney disease; MAP, mean arterial pressure; TKV, total kidney volume; *PKD1*, polycystic kidney disease 1; *PKD2*, polycystic kidney disease 2.

tan therapy are displayed in Table 1. The mean dose of tolvaptan was 54 mg in the *PKD1* truncating group, 77 mg in the *PKD1* non-truncating group, 60 mg in the *PKD2* group, and 60 mg in the no *PKD1/2* group. The dose was reduced in 3 patients (2 in the *PKD1* truncating group and 1 in the *PKD2* group) because of polyuria. No other additional adverse events including liver enzyme elevation, hypernatremia, and volume depletion were observed. The median follow-up period after starting treatment with tolvaptan was 3.8 years (IQR, 2.6–4.5 years) in the *PKD1* truncating group, 4.5 years (3.5–5 years) in the *PKD1* non-truncating group, 2.8 years (2.4–3.1 years) in the *PKD2* group, and 2.5 years (2–2.8 years) in the no *PKD1/2* group. We found no significant differences in age, BMI, mean atrial pressure, height-adjusted TKV, the number of cysts (in a middle section of the left kidney), or the follow-up period after starting treatment with tolvaptan between the groups. The patients with *PKD1* truncating mutations had significantly decreased eGFR than the other patients (Kruskal-Wallis, $p = 0.04$). Detailed information on the variants detected in the patients is presented in online suppl. Tables 1–4 (or all online suppl. material, see www.karger.com/doi/10.1159/000509817 f).

Influence of Gene Mutation on the Efficacy of Tolvaptan Therapy

Figure 1 shows the change in eGFR before and after tolvaptan therapy. We found no changes in variables that

may have influenced eGFR, including the use of an angiotensin 2 receptor blocker, before and after tolvaptan therapy. Urine osmolality, a surrogate of the efficacy of tolvaptan, did not differ between the groups before and after treatment (Table 2). The annual change in eGFR (Δ eGFR/y) from before to after tolvaptan therapy was from a median of -5.5 (IQR, -5.7 to -4.4) to -2.5 (-3.1 to -1.9) mL/min/1.73 m² in the *PKD1* truncating group, -3.3 (-4.6 to -2.4) to -2.4 (-3.9 to -2.0) mL/min/1.73 m² in the *PKD1* non-truncating group, -3.1 (-3.5 to -2.4) to -1.6 (-2.4 to -0.5) mL/min/1.73 m² in the *PKD2* group, and -1.9 (-2.6 to -1.2) to -2.6 (-3.3 to -1.8) mL/min/1.73 m² in the no *PKD1/2* group (Table 2). The median degree of improvement of Δ eGFR/y was 2.5 (45%) (IQR, 1.8–2.9) mL/min/1.73 m² in the *PKD1* truncating group, 0.4 (10%) (-0.2 –1.6) mL/min/1.73 m² in the *PKD1* non-truncating group, 0.6 (28%) (0.5–1.7) mL/min/1.73 m² in the *PKD2* group, and -0.7 (-37%) (-0.7 to -0.6) mL/min/1.73 m² in the no *PKD1/2* group (Fig. 2a). Compared with the *PKD1* truncating group, the no *PKD1/2* group showed significantly less improvement of Δ eGFR/y with tolvaptan ($p = 0.03$). Compared with the *PKD1* non-truncating group, the no *PKD1/2* group showed significantly less improvement of Δ eGFR/y with tolvaptan ($p = 0.04$). Compared with the *PKD2* group, the no *PKD1/2* group showed significantly less improvement of Δ eGFR/y with tolvaptan ($p = 0.03$). We found no significant differences in the changes in Δ eGFR/y before and after tolvaptan therapy

Fig. 1. Summary of changes in eGFR before and after tolvaptan therapy. Red line: *PKD1* truncating group ($n = 4$); *PKD1* tr ①~④, blue line: *PKD1* non-truncating group ($n = 7$); *PKD1* non-tr ①~⑦, green line: *PKD2* group ($n = 4$); *PKD2* ①~④, yellow line: no *PKD1*/*PKD2* group ($n = 3$); no *PKD1/2* ①~③. eGFR, estimated glomerular filtration rate; *PKD1*, polycystic kidney disease 1; *PKD2*, polycystic kidney disease 2.

Table 2. Summary of clinical and laboratory data before and after tolvaptan therapy

	<i>PKD1</i> truncating, $n = 4$	<i>PKD1</i> non-truncating, $n = 7$	<i>PKD2</i> , $n = 4$	No <i>PKD1/2</i> , $n = 3$
Urine osmolarity [before]	420 [410–430]	427 [281–560]	519 [393–642]	497 [441–524]
Urine osmolarity [after]	220 [205–282]	218 [180–236]	183 [180–236]	195 [168–221]
Δ eGFR/y, mL/min/1.73 m ² [before]	–5.5 [–5.7 to –4.4]	–3.3 [–4.6 to –2.4]	–3.1 [–3.5 to –2.4]	–1.9 [–2.6 to –1.2]
Δ eGFR/y, mL/min/1.73 m ² [after]	–2.5 [–3.1 to –1.9]	–2.4 [–3.9 to –2.0]	–1.6 [–2.4 to –0.5]	–2.6 [–3.3 to –1.8]
% Δ TKV/y, % [before]	5.9 [5.6–6.0]	7.1 [5.6–7.2]	7.8 [7.2–9.0]	5.3 [5.2–6.7]
% Δ TKV/y, % [after]	0.2 [–3.4–3.1]	0.3 [–0.4–2.8]	–1.1 [–5.5–3.3]	4.3 [3.5–5.7]

Data are expressed as number (percentage) or median [25th–75th percentiles]. eGFR, estimated glomerular filtration rate; Δ eGFR/y, the annual change in eGFR; TKV, total kidney volume; % Δ TKV/y, the annual rate of TKV increase; *PKD1*, polycystic kidney disease 1; *PKD2*, polycystic kidney disease 2.

Fig. 2. a Improvement in the annual change in $\Delta eGFR/y$ (mL/min/1.73 m²) with tolcapton therapy by genotype. Improvement of $\Delta eGFR/y = (\Delta eGFR/y \text{ after tolcapton}) - (\Delta eGFR/y \text{ before tolcapton})$. **b** Improvement in the annual change in $\Delta eGFR/y$ (mL/min/1.73 m²) with tolcapton therapy, PKD1/2 group versus no PKD1/2 group. Improvement of $\Delta eGFR/y = (\Delta eGFR/y \text{ after tolcapton}) - (\Delta eGFR/y \text{ before tolcapton})$. **c** Percentage improvement in the annual rate of TKV increase ($\Delta TKV/y$) with tolcapton therapy, PKD1/2 group versus no PKD1/2 group. Improve-

ment of $\Delta TKV/y = (\Delta TKV/y \text{ after tolcapton}) - (\Delta TKV/y \text{ before tolcapton})$. **d** Percentage improvement in the annual rate of TKV increase ($\Delta TKV/y$) with tolcapton therapy by genotype. Improvement of $\Delta TKV/y = (\Delta TKV/y \text{ after tolcapton}) - (\Delta TKV/y \text{ before tolcapton})$. $\Delta eGFR/y$, the annual change in estimated glomerular filtration rate; $\Delta TKV/y$, the annual rate of total kidney volume increase; PKD1, polycystic kidney disease 1; PKD2, polycystic kidney disease 2.

between the groups with a PKD1 truncating, PKD1 non-truncating, or PKD2 mutation. The no PKD1/2 group showed significantly less improvement of $\Delta eGFR/y$ than the group of patients with any PKD1/2 mutation (-0.7 vs. 0.6 mL/min/1.73 m², respectively; $p = 0.01$, Fig. 2b).

The annual rate of TKV increase ($\Delta TKV/y$) improved significantly less in the no PKD1/2 group than in the group of patients with any PKD1/2 mutation (-1.1 vs. -6.7% , respectively; $p = 0.02$, Fig. 2c). The median $\Delta TKV/y$ in each of the 4 mutation groups from before

to after tolvaptan therapy was as follows: *PKD1* truncating group, 5.9% (IQR, 5.6–6.0%) to 0.2% (–3.4 to 3.1%); *PKD1* non-truncating group, 7.1% (5.6–7.2%) to 0.3% (–0.4 to 2.8%); in the *PKD2* group, 7.8% (7.2–9.0%) to –1.1% (–5.5 to 3.3%); and in the no *PKD1/2* group, 5.3% (5.2–6.7%) to 4.3% (3.5–5.7%) (Table 2). The median degree of improvement of $\Delta\text{TKV}/\text{y}$ was –5.9% (IQR, –2.9 to –9.2%) in the *PKD1* truncating group, –5.4% (–3.8 to –6.9%) in the *PKD1* non-truncating group, –10.7% (–6.6 to –13.6%) in the *PKD2* group, and –1.1% (–1.0 to –1.9%) in the no *PKD1/2* group (Fig. 2d). We found no significant differences between the groups in the changes in $\Delta\text{TKV}/\text{y}$ before and after tolvaptan therapy.

Discussion

In the current study of 18 patients with ADPKD, $\Delta\text{eGFR}/\text{y}$ and $\Delta\text{TKV}/\text{y}$ improved less with tolvaptan therapy in the group without any variants in *PKD1* or *PKD2* than in the group with a mutation in one of these genes (*PKD1* truncating, *PKD1* non-truncating, or *PKD2*). The efficacy of tolvaptan therapy was investigated in several randomized, double-blind, placebo-controlled, multicenter, phase 3 trials, including the TEMPO 3:4 trial [6]; its long-term extension, the TEMPO 4:4 trial [7]; and the trial in later-stage ADPKD, REPRISE [8]. A post hoc analysis of data from TEMPO 4:4 found statistically significant treatment effects of tolvaptan in the *PKD1* truncating group but not in the *PKD1* non-truncating or *PKD2* group [7]. Unlike the TEMPO 4:4 study, which compared tolvaptan-treated with placebo-treated patients, the current study analyzed the change in $\Delta\text{eGFR}/\text{y}$ and $\Delta\text{TKV}/\text{y}$ before to after tolvaptan within patients. For this reason, our results are not directly comparable with those of the TEMPO 4:4 study. However, our study showed efficacy of tolvaptan not only in the *PKD1* truncating group but also in the *PKD1* non-truncating and *PKD2* groups. The important finding of our study is that the patients with ADPKD who had no *PKD1/2* mutation showed significantly less improvement of $\Delta\text{eGFR}/\text{y}$ and $\Delta\text{TKV}/\text{y}$ before to after tolvaptan therapy.

The vasopressin V2-receptor antagonist tolvaptan was effective in a *Pkd1*-deletion mouse model and *Pkd2*-deletion mouse model of ADPKD [17, 18], so its efficacy may be associated with the *PKD1/2* mutations found in patients with ADPKD. At present, *PKD1/2* mutations are not considered when administering tolvaptan therapy, but our findings suggest that in the future, physicians may need to test for them. In fact, the ERA-EDTA Working

Group already recommended adding a *PKD1* truncating mutation to the criteria for selecting tolvaptan therapy to treat patients with ADPKD [19].

The current study has some limitations. It was a retrospective, single-center study with a small sample size. Furthermore, it may have a selection bias because we included only patients who underwent genetic testing. Genetic testing is not commonly performed in Japan, but it is often performed in patients without an apparent family history. Thus, approximately 200 patients were treated with tolvaptan in our hospital, but genetic testing was performed in only 21 of them. Therefore, our findings need to be confirmed in a large, prospective, multicenter study. Despite these limitations, the study still led to the interesting finding that the efficacy of tolvaptan seems to differ between patients with ADPKD with no *PKD1/PKD2* mutation and typical ADPKD patients with a *PKD1/PKD2* mutation.

In conclusion, $\Delta\text{eGFR}/\text{y}$ and $\Delta\text{TKV}/\text{y}$ improved significantly less with tolvaptan therapy in the group without any detectable *PKD1/PKD2* mutation than in the group of patients with a mutation in one of these genes (*PKD1* truncating, *PKD1* non-truncating, or *PKD2*). Accordingly, determining whether or not patients with ADPKD have a *PKD1/PKD2* mutation may help predict the efficacy of tolvaptan therapy.

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The manuscript was checked by a native English-speaking medical editor from Yamada Translation Bureau, Inc. (Tokyo, Japan).

Statement of Ethics

This study was carried out in accordance with the Declaration of Helsinki and was approved by the research Ethics Committees of Toranomon Hospital and Tokyo Medical and Dental University Hospital. Written informed consent was obtained from all of the patients.

Conflict of Interest Statement

J.H. has received a research grant from Otsuka Pharmaceutical Co. All other authors have no competing financial interests to declare.

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Author Contributions

A.S., J.H., K.T., and Y.U. designed the study; A.S., J.H., T.S., H.M., M.K., R.H., E.H., M.Y., N.H., and N.S. managed the patients and collected clinical data; A.S., J.H., and Y.U. analyzed the genetic and clinical data; T.F., S.M., M.C., H.K., F.A., T.M., E.S., and S.U. analyzed gene mutations; A.S. made the figures and tables; and all authors approved the final version of the manuscript.

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