Original Article

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KIDNEY RESEARCH AND CLINICAL PRACTICE

Evaluating the Safety and effectivenesS in adult KorEaN patients treated with Tolvaptan for management of autosomal domInAnt poLycystic kidney disease (ESSENTIAL): final report

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Background: Tolvaptan, a selective vasopressin V2 receptor antagonist, was first approved by the Korean Ministry of Food and Drug Safety in 2015 as a treatment option for autosomal dominant polycystic kidney disease (ADPKD). To prescribe tolvaptan safely and effectively, we designed the phase 4 clinical trial among Korean ADPKD patients with chronic kidney disease stages 1 to 3.

Methods: A total of 117 Korean patients aged 19 to 50 years with rapidly progressing ADPKD were enrolled in the study. Tolvaptan was prescribed for 24 months with the maximum tolerable dose up to 120 mg/day. The primary outcome was the incidence of treatment-emergent adverse events (TEAEs) including hepatic adverse events. The secondary outcomes were the annual mean percent change of total kidney volume (TKV) and the annual mean change of estimated glomerular filtration rate (eGFR).

Results: A total of 489 TEAEs occurred in 106 patients (90.6%). A total of 17 cases of hepatic adverse events (14.5%) occurred during the study period and mostly within the first 18-month period. However, liver enzymes were normalized after drug discontinuation. Although it was not statistically significant, patients with a previous history of liver disease as well as those with mild elevation of liver enzyme showed a higher frequency of hepatic adverse events. Compared with the predicted value from the calculation, tolvaptan attenuated both TKV growth and eGFR decline rate.

Conclusion: Although the incidence of hepatic adverse events was higher in Korean ADPKD patients compared to the previous studies, tolvaptan can be prescribed safely and effectively using meticulous titration and 1-month interval monitoring.

Keywords: Autosomal dominant polycystic kidney, Chemical and drug induced liver injury, Drug-related side effects and adverse reactions, Glomerular filtration rate, Treatment outcome, Tolvaptan

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease leading to end-stage kidney disease [1]. Tolvaptan, a selective vasopressin V2 receptor antagonist, is the only U.S. Food and Drug Administration-approved drug for reducing cyst growth and attenuating renal function decline [2]. The result from the phase 3 TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4) trial demonstrated that tolvaptan could slow the increase in total kidney volume (TKV) and the decline in kidney function in the patients with chronic kidney disease (CKD) stages 1 and 3 [3]. The subsequent clinical trial named the REPRISE (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD) demonstrated that the efficacy and safety of tolvaptan was maintained even in patients with the advanced CKD stages [4]. The common adverse effects of tolvaptan are aquaresis-related symptoms and hepatotoxicity [5]. In the earlier clinical trial such as TEMPO 3:4, the monitoring interval was 4 months [3]. However, since tolvaptan can cause serious hepatotoxicity and frequent dropouts related to adverse effects, the monitoring interval during treatment has been shortened to every 1 month [4,6,7].

Tolvaptan was first approved by the Korean Ministry of Food and Drug Safety in 2015 as a treatment option for rapidly progressive ADPKD and has been covered by the National Health Insurance since 2019 in Korea [8]. Since 2019, the number of newly diagnosed patients and subsequent tolvaptan prescriptions has been increasing. However, the population included in the TEMPO 3:4 trial was mainly Caucasian and the proportion of Asians was minimal [3]. In order to prescribe tolvaptan in Korean ADPKD patients safely and effectively, we designed a phase 4 clinical trial called the ESSENTIAL (Evaluating the Safety and effectiveneSs in adult KorEaN patients treated with tolvaptan for management of autosomal domInAnt poLycystic kidney disease) among Korean ADPKD patients with CKD stages 1 to 3 [9]. The purpose of this study was to investigate the safety and effectiveness of tolvaptan in Korean ADPKD patients with CKD stages 1 to 3 and the evidence of rapid progression. The short-term outcome of this study was published elsewhere [9], and this is the final report of this clinical trial.

Methods

Study population and study design

This was a multicenter, single-arm, open-label, phase 4 clinical trial. The trial design and setting were previously described in detail [9]. We enrolled Korean patients aged 19 to 50 years with rapidly progressing ADPKD who have never been exposed to tolvaptan. The rapidly progressing ADPKD was defined by one of the followings: Mayo imaging classification 1C to 1E [10], *PKD1* truncating mutation, PROPKD (Predicting Renal Outcome in Polycystic Kidney Disease) score ≥6, or decrease in estimating glomerular filtration rate (eGFR) of more than 5 mL/min/1.73 m^2 in 1 year or 2.5 mL/min/1.73 m^2 in 5 years.

The patients with one of the followings were excluded from the study: patients with hyponatremia or hypernatremia, anuric patients, patients with volume depletion, patients who cannot feel thirst or cannot adequately respond to the sense of thirst, patients with contraindication to magnetic resonance imaging (MRI) exam, patients with severe renal or hepatic impairment, patients with previous allergic history to tolvaptan or derivatives, patients with galactose intolerance, patients who need long-term diuretic therapy, patients with other causes of renal function decline, women with pregnancy or lactation, and those who decline to participate in the study by written informed consent.

The screening for patient selection was performed at a maximum of 8 weeks before drug prescription, and the dose titration was performed every 1 week for a total of 4 weeks. The patient was prescribed tolvaptan with a maximum tolerable dose up to 120 mg per day. The total duration of tolvaptan prescription was 24 months. The last follow-up visit was within 7 days of the last drug prescription. The study design is demonstrated in Fig. 1.

This study was registered at clinicaltrials.gov before patient enrollment (NCT 03949894). The study protocol was approved by the Institutional Review Board (IRB) of each participating hospital (representative hospital IRB No. H-1902-041-1009), and written informed consent was obtained from each patient before enrollment. The study was performed according to the Declaration of Helsinki.

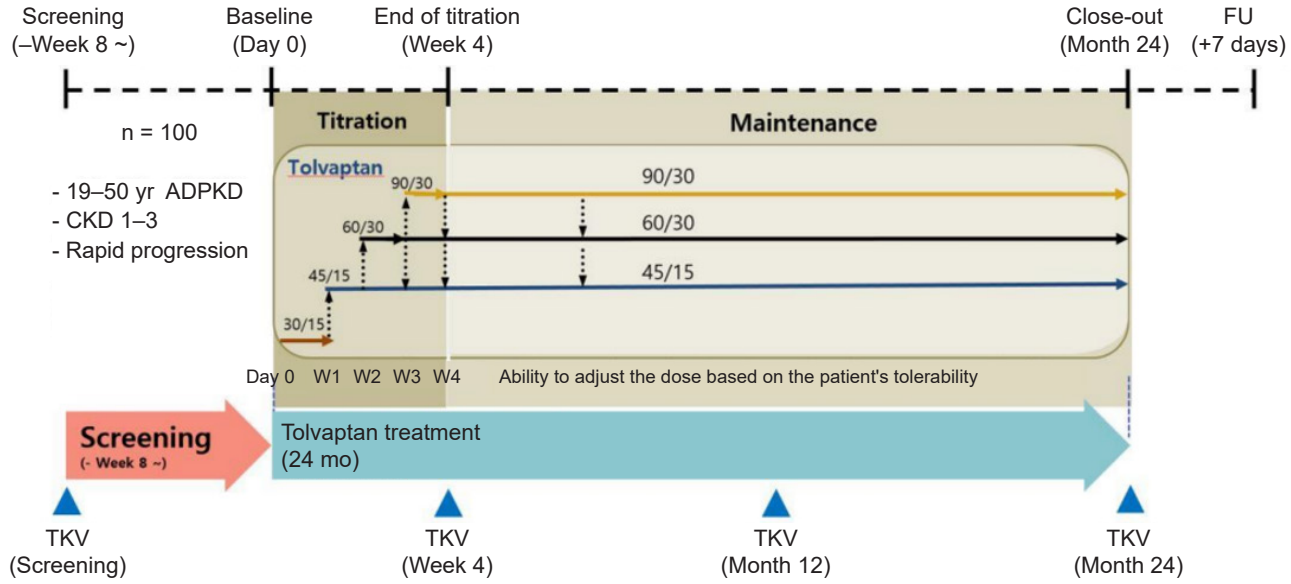


Figure 1. Study design. This was a multicenter, single-arm, open-label, phase 4 clinical trial to evaluate the safety and effectiveness of tolvaptan among Korean patients with rapidly progressive autosomal dominant polycystic kidney disease (ADPKD). Subjects who met inclusion criteria through a screening period up to 8 weeks underwent a 4-week titration period to check tolerability to tolvaptan treatment. The subjects received tolvaptan for 2 years with the maximum tolerable dose of 120 mg per day. Subjects followed the specified procedures at each regular visit. Whether the subjects completed a 2-year administration of drug or not, all patients were subjected to the last follow-up visit (visit 26) to confirm the safety and effectiveness of tolvaptan treatment.
CKD, chronic kidney disease; FU, follow-up; TKV, total kidney volume, W, week.

Outcome measures

The primary outcome was the incidence of treatment-emergent adverse events (TEAEs) which includes liver injury (elevation of alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level > three times the upper limit of the normal range, or elevation of total bilirubin > two times the upper limit of the normal range), adverse events leading to death, serious adverse events, adverse events leading to treatment discontinuation, adverse events whose causal relationship with the study drug cannot be ruled out, severe adverse events, and the adverse events such as dehydration, dysnatremia, and creatinine elevation. The secondary outcomes were the annual mean percent change of TKV and the annual mean change of eGFR. For outcome measurement, the subjects underwent MRI of the abdomen four times (screening, at 4 weeks, at 1 year, and at 2 years) to measure TKV. TKV was measured from the central image analysis center (Lingovia, Inc.) from MRI acquired from each center. The change in TKV was measured from the difference between TKV at the last treatment (visit 25) and TKV at the screening period (baseline TKV). Serum creatinine was measured every visit from the central laboratory from which eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) equation [11]. The change in eGFR was measured in two ways. The off-treatment outcome was measured from the difference between eGFR at baseline and eGFR at the last follow-up (visit 26). The on-treatment outcome was measured from the difference between eGFR at the last dose-titration point (visit 6) and the last treatment (visit 25).

Statistical analysis

The sample size for this clinical trial was calculated in the following manner. In the previous TEMPO 3:4 clinical trial, the incidence of elevation in ALT more than three times the upper limit of the normal range was 4.4%. Therefore, one in every 23 patients will experience the elevation of ALT in theory. To determine the target number with a 95% confidence interval, 69 test subjects were needed using the rule of three. Expecting a dropout rate of 30%, we calculated the

sample size as 100 patients.

The safety outcome was measured among the patients who received tolvaptan at least once (safety analysis set). The efficacy outcomes (annual TKV growth rate or annual eGFR decline rate) were measured among those with at least one outcome measure (full analysis set). In order to calculate the annual TKV growth rate, the TKV was $\log_{10}$-transformed and then the annual percent change of TKV was calculated using a linear mixed model. The time frame was calculated from (last TKV measured date – baseline TKV measured date) / 365.25. The measured annual growth rate of height-adjusted TKV was compared with the predicted measure from the following equation: $100 \times [\{(\text{baseline TKV} / \text{baseline height}) / 150\}^{(1 / \text{baseline age})} - 1]$ [10]. The annual eGFR decline rate was calculated similarly to the annual TKV growth rate using a linear mixed model and was compared with the estimated eGFR change from the prediction model from the previous study [10].

Statistical analysis was conducted using the SAS version 9.4 (SAS Institute). For descriptive analysis, data were represented as mean ± standard deviation for continuous variables and frequencies for categorical variables. The continuous variables without normal distribution were described as median (first quartile, third quartile). Since this study is not a controlled study, we compared the outcomes between subgroups according to sex, baseline CKD stages, Mayo imaging classification, and body mass index. A mixed model repeated measure was used for efficacy analysis. A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

A total of 117 patients were included in the safety analysis set. The baseline characteristics of the patients are described in Table 1. The mean age of the subjects was 38.7 ± 8.4 years and male sex was predominant (n = 68, 58.1%). Most of the patients (n = 100, 85.5%) had hypertension. The mean TKV was 2,066 ± 1,094 mL and the mean eGFR was 79.7 ± 27.7 mL/min/1.73 m^2. The proportion of Mayo class 1C, 1D, 1E was 34.2%, 33.3%, and 31.6%, respectively.

The mean duration of tolvaptan exposure was 1.7 ± 0.6 years. The average daily dose of tolvaptan was 94.4 ± 24.1 mg/day and the mean weight-adjusted daily dose was 1.3 ± 0.5 mg/kg/day. At the end of the titration period, 69 patients (62.7%) were taking 120 mg of tolvaptan per day. About 50.5% of the patients also maintained the maximum dose of 120 mg at the end of the trial.

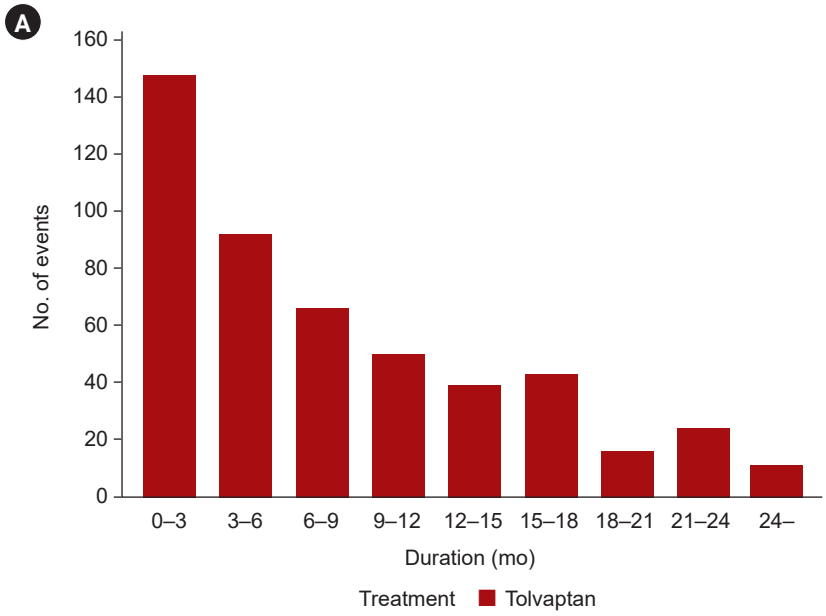
Safety outcome

A total of 489 TEAEs occurred in 106 patients (90.6%) during the study duration. Nearly half of the TEAEs occurred within the first 6 months of the study (Fig. 2A). Common TEAEs that occurred in >5% population are described in Table 2. The hepatic adverse events and aquaresis-related adverse

Table 1. Baseline characteristics of the patients in the safety analysis set

Characteristic	Data
No. of patients	117
Age (yr)	38.7 ± 8.4
Male sex	68 (58.1)
Body mass index (kg/m^2)	25.2 ± 4.2
Systolic blood pressure (mmHg)	128.8 ± 13.7
Diastolic blood pressure (mmHg)	82.9 ± 10.5
Hypertension	100 (85.5)
ACE inhibitor/ARB	104 (88.9)
Statin	46 (39.3)
TKV (mL)	2,066 ± 1,094
Height-adjusted TKV (mL/m)	1,211 ± 622
Mayo image classification	
1B	1 (0.9)
1C	40 (34.2)
1D	39 (33.3)
1E	37 (31.6)
Serum creatinine (mg/dL)	1.2 ± 0.5
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	79.7 ± 27.7
CKD stage	
Stage1	48 (41)
Stage 2	35 (29.9)
Stage 3	33 (28.2)
Stage 4	1 (0.9)
Duration of exposure (yr)	1.7 ± 0.6
Average dose of exposure (mg/day)	94.4 ± 24.1
Weight-adjusted dose (mg/kg/day)	1.3 ± 0.5

Data are expressed as number only, mean ± standard deviation, or number (%).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CKD-EPI, CKD-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; TKV, total kidney volume.



	Total	0–3	3–6	6–9	9–12	12–15	15–18	18–21	21–24	24–
TEAEs (n)	489	148	92	66	50	39	43	16	24	11
Cumulative (%)	100	30	49	63	73	81	90	93	98	100

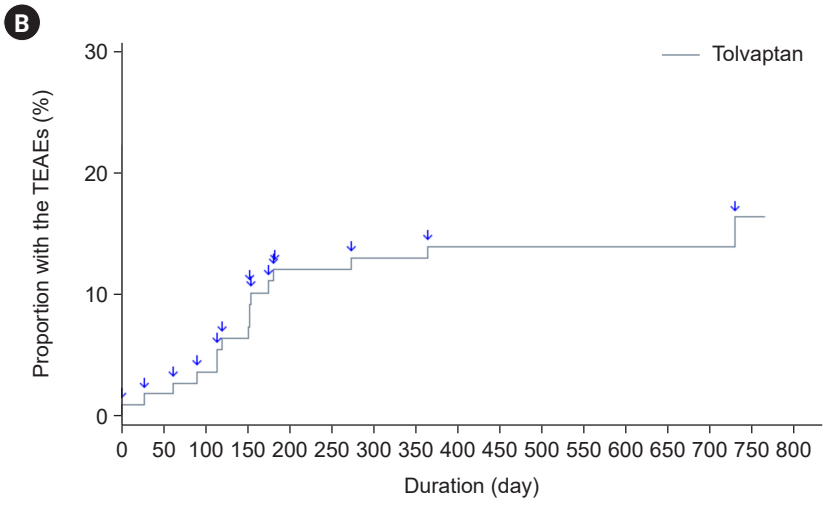


Figure 2. The safety profile of tolvaptan among Korean patients with autosomal dominant polycystic kidney disease. (A) A total of 489 treatment-emergent adverse events (TEAEs) occurred in 90.6% of the subjects during the 2 years of study period. Nearly half of the TEAEs occurred within 6 months of the study. (B) A total of 17 hepatic adverse events (14.5%) occurred during the study period. Most of the cases occurred within the first 18 months. Arrows means the time to the first adverse drug reaction related liver injury.

events were the two most common adverse events. Elevation in ALT occurred in 45 cases in 26 patients (22.2%). A total of 17 cases (14.5%) with the elevation of ALT or AST level > three times the upper normal limit (UNL) or elevation of total bilirubin > two times UNL occurred during the study period. There was only one case of adverse events related to Hy's law (Table 3). However, the liver enzymes were normalized after drug discontinuation.

Hepatic adverse events occurred more frequently within 18 months (Fig. 2B). Although it was not statistically

significant, patients with previous history of liver disease such as fatty liver (33.3% vs. 12.4%, p = 0.07) (Fig. 3A) or mild elevation of ALT/AST or bilirubin (26.1% vs. 11.7%, p = 0.10) (Fig. 3B) demonstrated higher frequency of hepatic adverse events. The frequency of hepatic adverse events was not different according to either Mayo imaging classification (7.5% in 1C, 23.1% in 1D, 13.5% in 1E; p = 0.14) (Fig. 3C) or CKD stages (14.6% in stage 1, 17.1% in stage 2, 12.1% in stage 3; p = 0.84) (Fig. 3D). The frequency of hepatic adverse events also did not differ according to the average dose of tolvaptan (10.9% in those taking < 90 mg/day vs. 17.7% in those taking ≥ 90 mg/day, p = 0.30).

Table 2. Treatment-emergent adverse events during tolvaptan use (>5%)

Treatment-emergent adverse events	Patients with event
ALT increased	26 (22.2)
AST increased	17 (14.5)
Headache	16 (13.7)
Thirst	14 (12.0)
Polyuria	13 (11.1)
Nocturia	12 (10.3)
Dyspepsia	11 (9.4)
Diarrhea	9 (7.7)
Pollakiuria	9 (7.7)
Nasopharyngitis	9 (7.7)
Nausea	8 (6.8)
Fatigue	8 (6.8)
Dizziness	8 (6.8)
Renal pain	7 (6.0)
Hypertension	7 (6.0)
Anemia	7 (6.0)
Constipation	6 (5.1)
Influenza	6 (5.1)
Blood creatinine increased	6 (5.1)

Data are expressed as number (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

There were no cases of patient death. There were eight patients (6.8%) who decided to discontinue tolvaptan treatment due to adverse events. The most common cause of drug discontinuation was hepatic adverse events accounting for 10 cases in five patients (4.3%) (Supplementary Table 1, available online). Other causes of treatment discontinuation were pruritus/rash, aquaresis-related issue, renal cyst infection, and difficulty in defecation. A total of 33 patients (28.2%) reported dehydration and six patients (5.1%) reported increased creatinine. However, there were no TEAE related to hyponatremia or hypernatremia.

Tolvaptan effect on total kidney volume

Among 109 patients with available TKV measurements from baseline up to 24 months, the annual growth rate of TKV was calculated. A linear mixed model with $\log_{10}$-transformation was used to calculate the estimated slope of

Table 3. Comparison of liver injury incidence after tolvaptan use among clinical trials

Variable	Trial				
	ESSENTIAL	TEMPO 3:4		REPRISE	
Study duration (yr)	2	3		1	
Monitoring interval	1-month interval until 18 months, 3-month interval thereafter	Every 4 months		Every month	
Subjects	Tolvaptan (n = 117)	Tolvaptan (n = 958)	Placebo (n = 484)	Tolvaptan (n = 681)	Placebo (n = 685)
ALT > 3 × ULN	15 (12.8)	42 (4.4)	5 (1.0)	38 (5.6)	8 (1.2)
ALT or AST > 3 × ULN or TB > 2 × ULN	17 (14.5)	48 (5.0)	11 (2.3)	41 (6.0)	8 (1.2)
ALT or AST > 3 × ULN and TB > 2 × ULN	1 (0.9)	2 (0.2)	0 (0)	0 (0)	0 (0)
ALT or AST > 3 × ULN and TB > 2 × ULN and ALP < 2 × ULN	1 (0.9)	2 (0.2)	0 (0)	0 (0)	0 (0)

Data are expressed as number (%) unless otherwise specified.
ESSENTIAL, Evaluating the Safety and effectivenesS in adult KorEaN patients treated with tolvaptan for management of autosomal domInAnt poLycystic kidney disease; REPRISE, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD; TEMPO 3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ULN, upper limit of normal.

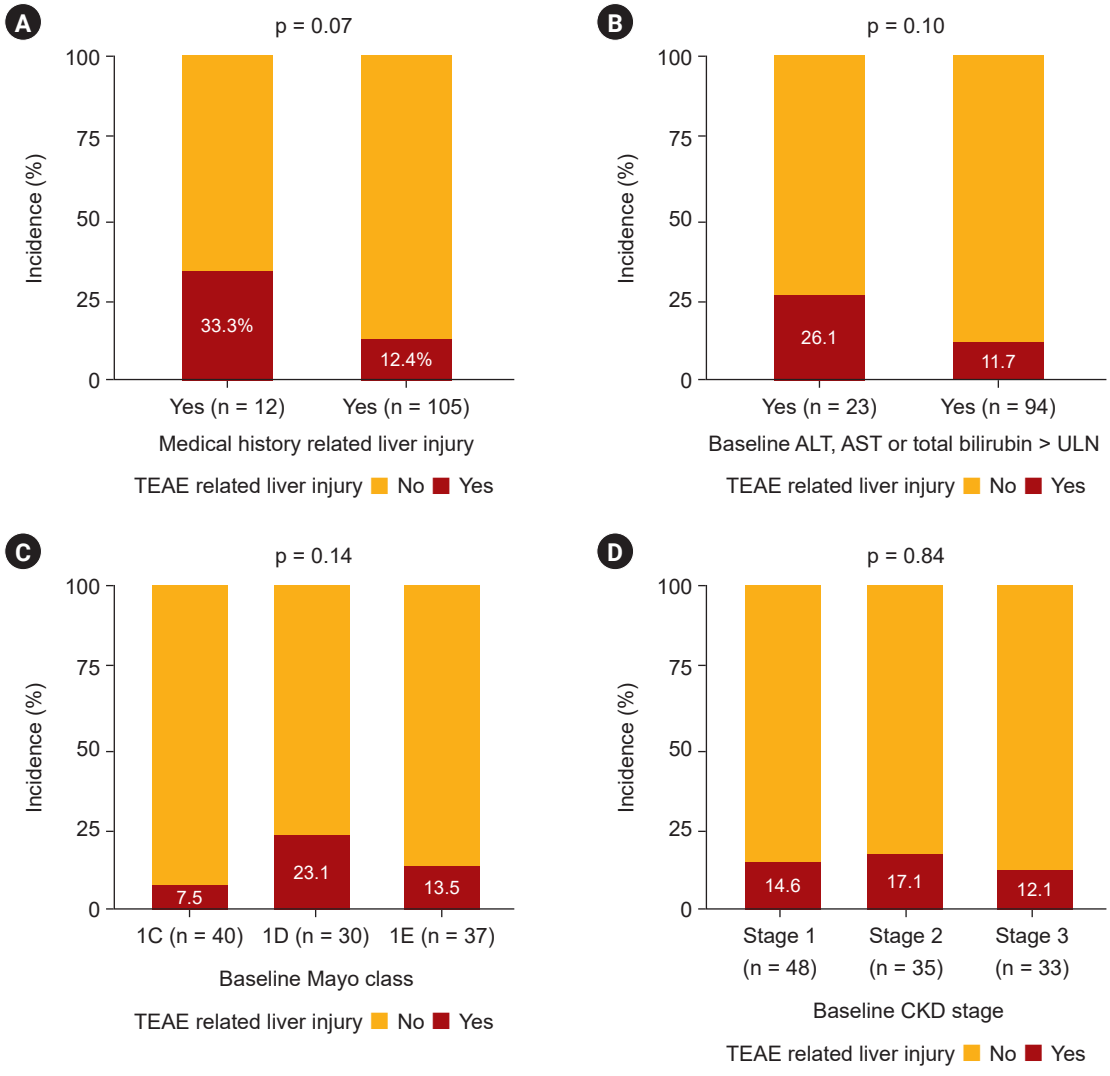


Figure 3. Incidence of hepatic adverse events according to subgroups. (A) Patients with a medical history of liver disease showed a higher tendency of hepatic adverse events with marginal statistical significance (33.3% vs. 12.4%, p = 0.07). (B) Patients with elevated liver enzymes before taking tolvaptan demonstrated a higher tendency of hepatic adverse events without statistical significance (26.1% vs. 11.7%, p = 0.10). (C) There was no difference in hepatic adverse events according to Mayo imaging classification (p = 0.14). (D) There was no difference in hepatic adverse events according to chronic kidney disease (CKD) stages (p = 0.84).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse events; ULN, upper limit of normal.

TKV growth. The mean growth rate of TKV among tolvaptan-treated patients was 4.5% ± 0.5%. The tolvaptan effect to attenuate kidney growth was the largest at the end point of titration (–2.3% ± 1.0%) and decreased thereafter (1.2% ± 1.2% at 1-year and 8.6% ± 1.5% at 2-year) (Fig. 4A). When compared with the predicted value of height-adjusted TKV growth rate from calculation [10], the measured TKV growth rate was slower than the predicted value (4.45% ± 5.66% vs. 5.45% ± 1.89%, p = 0.06).

Since the TEMPO 3:4 trial only included a few Asian populations (mostly Japanese patients), we compared our results with our historical ADPKD cohort [12] who had not received tolvaptan treatment before (Supplementary Table 2, available online). Korean ADPKD patients without tolvaptan treatment showed a larger TKV growth rate according to Mayo imaging classification compared to those

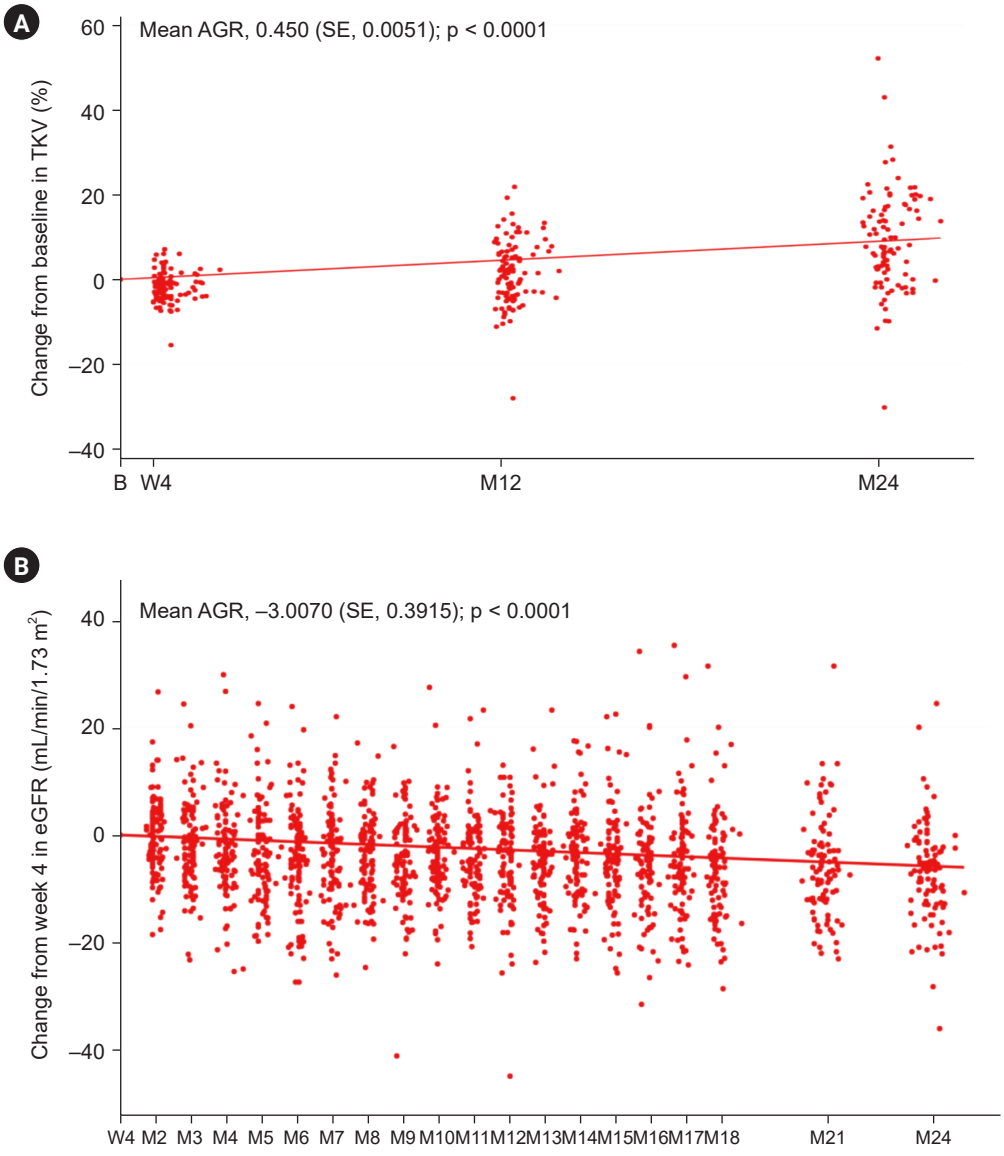


Figure 4. Effect of tolvaptan upon TKV and eGFR. (A) The mean annual growth rate (AGR) of TKV among tolvaptan-treated patients was 4.5% ± 0.5%. The tolvaptan effect to attenuate kidney growth was the largest at the end point of titration (–2.3% ± 1.0%) and decreased thereafter (1.2% ± 1.2% at 1 year and 8.6% ± 1.5% at 2 years). (B) The on-treatment effect was calculated using the annual eGFR decline rate from the completion of the tolvaptan titration period to the end of the treatment visit (3.0 ± 0.39 mL/min/1.73 m^2/yr). (C) The off-treatment effect was calculated using the annual eGFR decline rate from baseline to the follow-up visit (–3.09 ± 0.38 mL/min/1.73 m^2/yr). A linear mixed model with log_{10}-transformed as TKV data and (date of MRI visit – date of MRI visit at baseline) / 365.25 as time.

B, baseline; eGFR, estimated glomerular filtration rate; FU, follow-up; M, month; MRI, magnetic resonance imaging; SE, standard error; TKV, total kidney volume; W, week. (Continued to the next page)

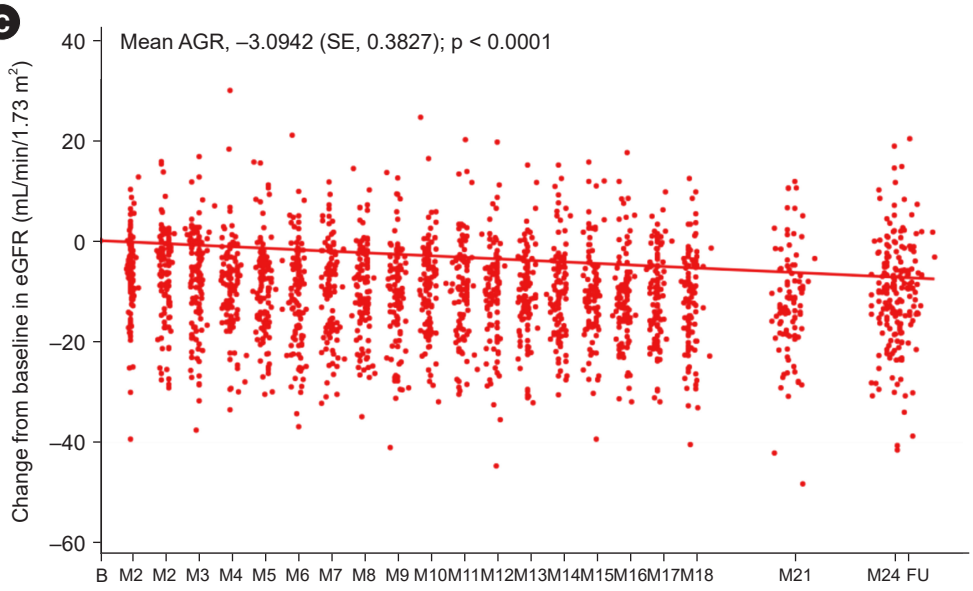


Figure 4. Continued.

in the TEMPO 3:4 trial (KNOW-CKD [KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease] vs. TEMPO 3:4 placebo group: 5.26% vs. 5.12% in class 1C, 9.39% vs. 5.62% in class 1D, 11.72% vs. 7.75% in class 1E). Compared to the natural TKV growth rate in historical cohort, tolvaptan use in the ESSENTIAL trial showed significant attenuation of TKV growth after 24 months of medication (Supplementary Table 2, available online).

Tolvaptan effect on estimated glomerular filtration rate

Tolvaptan treatment effect on the annual change in eGFR was measured in two ways: on-treatment and off-treatment. The on-treatment effect was calculated using the annual eGFR decline rate from the completion of the tolvaptan titration period to the end of the treatment visit. The off-treatment effect was calculated using annual eGFR decline rate from baseline to the follow-up visit. The on-treatment effect of tolvaptan on annual eGFR decline rate was –3.0 ± 0.39 mL/min/1.73 m^2/yr (Fig. 4B) while the off-treatment effect on annual eGFR decline rate was –3.09 ± 0.38 mL/min/1.73 m^2/yr (Fig. 4C). When compared with the predicted value of eGFR decline rate from prediction model [10], the measured annual eGFR decline rate was slower than the predicted value with marginal statistical significance (–3.77 ± 5.29 mL/min/1.73 m^2/yr vs. –4.75 ± 1.81 mL/min/1.73 m^2/yr, p = 0.06).

The eGFR decline rates according to Mayo imaging classification in the historical ADPKD cohort (KNOW-CKD cohort) were similar to those in the TEMPO 3:4 trial [12]. Tolvaptan use effectively attenuated renal function decline in the ESSENTIAL cohort compared to the values in the historical ADPKD cohort (Supplementary Table 3, available online). Especially, in the patients within Mayo imaging classification 1C, tolvaptan significantly decreased the renal function decline rate compared to the value in the nontreated group in the KNOW-CKD cohort (–1.22 mL/min/1.73 m^2/yr vs. –3.58 mL/min/1.73 m^2/yr).

Discussion

This is the first clinical trial assessing the safety and efficacy of tolvaptan in Korean patients with ADPKD. Our study demonstrated that the incidence of TEAE was not higher than that from the previous clinical trial (90.6% in our study and 97.9% in the TEMPO 3:4 trial) [3]. However, the incidence of hepatic adverse events was much higher than those from the previous studies (14.5% in our study, 5.0% in the TEMPO 3:4 trial, and 6.0% in the REPRISE trial) [3,4]. Although statistically insignificant, the patients with previous history of liver disease or those with elevated liver enzyme before prescribing tolvaptan showed a higher rate of

hepatic adverse events during the study period. However, hepatic adverse event was resolved after drug discontinuation and there was no patient death associated with hepatic adverse events by monthly monitoring. Although our study did not include a control group, tolvaptan effectively reduced the TKV growth rate as well as the renal function decline rate.

Our study, like previous studies, confirmed that tolvaptan can be prescribed safely and effectively using meticulous titration and 1-month interval monitoring [3,4,6,13]. As known previously, aquaresis-related adverse events and hepatic adverse events were two important side effects of tolvaptan use [5]. However, monitoring side effects at 1-month interval showed that even if side effects occurred, we can prevent severe TEAEs or patient death by reducing the dose of medication or discontinuing the drug.

One of the new findings in our ESSENTIAL trial was that the incidence of hepatic adverse events in Korean patients was much higher than those in the previous studies. In the TEMPO 3:4 trial, without 1-month interval monitoring of liver function, hepatic adverse events occurred in 5.0% of the patients (Table 3) [3]. In the REPRISE trial with patients with more advanced CKD, hepatic adverse events occurred in 6.0% of the patients [4]. However, our study demonstrated a much higher incidence of hepatic adverse events showing 14.5%. One of the possible explanations would be ethnic difference. Japanese subgroup analysis also demonstrated that 10.2% of the subjects experienced hepatic function abnormality during the study [14]. Another possible explanation would be that a large proportion of the patients (n = 23, 19.7%) already had a mild elevation of baseline AST, ALT, or total bilirubin before taking tolvaptan in our study. Although statistically insignificant, those with hepatic function abnormality showed a higher frequency of hepatic adverse events during the study period (26.1% vs. 11.7%, p = 0.10) (Fig. 3B). However, the number of patients with previous history of liver disease or elevated liver enzymes were small to demonstrate the statistically significant difference. Meanwhile, the development of hepatic adverse events is known to be not related to either CKD stages, TKV, or dose of prescription [15]. Our study also confirmed that hepatic adverse events are not dose-dependent and are unpredictable. There was one case meeting Hy's law to discontinue the drug. However, liver function recovered completely after drug discontinuation. Therefore, a 1-month monitoring interval for checking liver function abnormality is efficient for detecting hepatic adverse events and preventing acute liver failure.

The subjects in our study demonstrated larger baseline TKV compared to those in the TEMPO 3:4 trial (2,066 mL in our study vs. 1,705 mL in the tolvaptan arm and 1,668 mL in the placebo arm in the TEMPO 3:4 trial) [3]. In addition, the proportion of Mayo class 1E was higher in our study compared to that in the TEMPO 3:4 trial (31.6% vs. 18.8%) [16]. Moreover, the proportion of CKD stage 3 was higher compared to that in TEMPO 3:4 (28.2% vs. 17.0%) [17]. Therefore, the subjects included in our trial had advanced renal disease at baseline. Thus, the efficacy of tolvaptan in reducing TKV growth rate was lesser compared to tolvaptan arm in the TEMPO 3:4 trial (4.5% per year in the ESSENTIAL trial vs. 2.8% per year in the TEMPO 3:4 trial). However, when compared to the placebo arm in the TEMPO 3:4 trial, tolvaptan could effectively reduce the TKV growth rate even though the baseline TKV was much larger in our ESSENTIAL study group (4.5% per year in the ESSENTIAL trial vs. 5.51% per year in the placebo group in the TEMPO 3:4 trial). In addition, when we compared our result with the estimated TKV growth rate from the prediction model (pretreatment), tolvaptan treatment could effectively reduce the TKV growth rate. Although our study cohort included a larger proportion of the patients with advanced CKD stages, the annual eGFR decline rate was slower than that in the placebo group in the TEMPO 3:4 trial (–3.0 mL/min/1.73 m^2/yr vs. –3.7 mL/min/1.73 m^2/yr) [3]. In addition, when compared with the estimated eGFR decline rate in the prediction model (pretreatment), tolvaptan slowed down the renal function decline rate with marginal statistical significance (–3.77 ± 5.29 mL/min/1.73 m^2/yr vs. –4.75 ± 1.81 mL/min/1.73 m^2/yr, p = 0.06).

Our study has some limitations. This was not a placebo-controlled clinical trial, and therefore, we cannot directly compare the effect of tolvaptan on TKV and renal function between the treatment group and the control group. Instead, we compared our results with the results from a historical ADPKD cohort without treatment (KNOW-CKD cohort). Second, the number of patients was too small to generalize the result. Third, genotypic information and medical history to decide prognostic information was lacking. However, our study demonstrated the tolvaptan effect and safety profile in Korean ADPKD patients. Tolvaptan

can be prescribed safely and effectively using meticulous titration and 1-month interval monitoring.

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Conflicts of interest

Tae-Hyun Yoo is the Editor-in-Chief, and Seungyeup Han is an Associate Editor of *Kidney Research and Clinical Practice*. Soo Wan Kim was an Associate Editor at the time of submission and review. They were not involved in the review process of this article. All authors have no other conflicts of interest to declare.

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Data sharing statement

Data sharing requests will be considered on a case-by-case basis through internal evaluation process. The request can be sent through e-mail: kop-essential@kr.otsuka.com.

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