Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Autosomal-dominant polycystic kidney disease: tolvaptan use in adolescents and young adults with rapid progression

Rupesh Raina[1], Ronith Chakraborty[2], Meredith E. DeCoy[3] and Timothy Kline[4]

BACKGROUND: The phase 3 Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO 3:4) clinical trial demonstrated the beneficial effect of tolvaptan on kidney growth and function in subjects aged 18–50 years over a 3-year period. However, it did not specifically assess the use of tolvaptan in adolescents and young adults (AYAs) with ADPKD.

METHODS: A post hoc analysis of the TEMPO 3:4 trials was performed for patients aged 18–24 years. The primary outcome was the annual rate of change in total kidney volume (TKV). The secondary outcome was to evaluate long-term safety of tolvaptan using Hy's law of hepatotoxicity.

RESULTS: A total of 51 patients in the 18–24 age group were analyzed (tolvaptan: 29, placebo: 22). The tolvaptan group had a lower mean percentage of TKV growth per year compared to the placebo group (3.9% vs. 6.5%, $P = 0.0491$). For secondary outcomes, 63 patients in the AYA subgroup were evaluated. In both the AYA and adult groups, none of the patients met the criteria for Hy's law of hepatotoxicity.

CONCLUSIONS: This post hoc analysis suggests that tolvaptan, with appropriate patient selection and management, can provide effective and acceptably safe treatment in AYAs with ADPKD.

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IMPACT:

- Tolvaptan slows the increase in total kidney volume in patients aged 18–24 years with ADPKD.
- Tolvaptan posed no risk of potential liver injury measured via Hy's law of hepatotoxicity in the AYA stratum.
- This study suggests that tolvaptan has beneficial outcomes in AYAs.
- This post hoc analysis suggests the need for additional studies with a larger pediatric patient population.
- The impact is significant as tolvaptan had not been specifically examined in the AYA patient population previously.

INTRODUCTION

Autosomal-dominant polycystic kidney disease (ADPKD) is a common, inherited progressive kidney disease.[1] The pathogenesis involves development and progression of fluid-filled cysts, the production of which may be controlled by a hormone known as vasopressin, a powerful modulator of cystogenesis.[2,3] Cyst and kidney growth in ADPKD can impair kidney function, although patients with ADPKD may remain asymptomatic for years and appear stable over time while the disease progresses.[4] In addition to effects on the kidney, ADPKD is associated with extrarenal manifestations, complications, and a burden on healthcare resources.[5–7] Although kidney function is of limited value early in the course of the disease for predicting disease progression, total kidney volume (TKV) typically increases from the very early stages of ADPKD, usually long before renal function declines, and predicts later decline in glomerular filtration rate (GFR).[8,9]

Cysts in ADPKD are mainly derived from vasopressin-sensitive tubular segments expressing V_2 receptors, such as the medullary think ascending limb, macula densa, the distal nephron, and the collecting duct. The V_2 receptor is overexpressed in polycystic kidneys and circulating levels of vasopressin are elevated in ADPKD. Cyst epithelial cells are persistently stimulated to proliferate and secrete fluid due to elevated levels of vasopressin.[10]

Tolvaptan (JYNARQUE™ [USA]; Jinarc® [EU, Canada]; Samsca® [Japan])) is a selective vasopressin V_2 receptor antagonist recently approved by the US Food and Drug Administration (FDA) as the first and only treatment for ADPKD, with an indication to slow kidney function decline in adults at risk of rapidly progressing ADPKD.[11,12] Tolvaptan has been studied in two of the largest clinical trials conducted in patients with early- and late-stage ADPKD, respectively: the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO 3:4) and the Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE; NCT02160145).[13,14] In TEMPO 3:4, participants

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(age 18–50 years, $N = 1445$) were randomized in a 2:1 ratio to receive tolvaptan or placebo over a 3-year period. Tolvaptan significantly reduced the rate of change of TKV by 49% over 3 years and the most significant decrease in TKV was seen in the first year, compared to years 2 and 3. Tolvaptan also reduced the rate of estimated GFR (eGFR) decline at chronic kidney disease (CKD) stages 1–3 and the relative rate of ADPKD-related complications decreased by 13.5% with tolvaptan treatment.[13] In REPRISE, participants (age 18–65 years, $N = 1370$) were randomized 1:1 to tolvaptan or placebo for a 1-year period. Tolvaptan reduced the rate of eGFR decline in this population at CKD stage 2 to early stage 4, with a treatment effect of 1.3 mL/min/1.73 m^2/year.[14]

With this information and tolvaptan's recent approval in the United States in April 2018, pediatric nephrologists wanted to prescribe this medication to adolescent and young adults (AYAs) aged 18–24 years. Since there were no interim analyses to assess use of tolvaptan specifically in AYAs, healthcare providers have searched for data on the incidence of ADPKD cases; valid risk factors for rapid progression of ADPKD; and reliable, evidence-based practice for prescribing tolvaptan to young adults. Therefore, we report a post hoc analysis of the TEMPO 3:4 clinical trial investigating the role of tolvaptan in the management of ADPKD for patients aged 18–24 years.

METHODS

Trial design

This study was presented as a post hoc analysis of the prospective, blinded, and randomized TEMPO 3:4 trials (ClinicalTrials.gov identifier: NCT00428948, January 26, 2007), specifically the 18–24-year age group in comparison to the adult age group (25–50 years of age). Patients were enrolled during January 2007 to January 2009 from 129 sites worldwide. The enrollment criteria of the TEMPO 3:4 study included an age of 18–50 years, Cockcroft–Gault GFR > 60 mL/min, and TKV ≥ 750 L determined by magnetic resonance imaging (MRI). In the absence of Cockcroft–Gault GFR, an estimate based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation of >45 mL/min was used, and in the absence of TKV, ultrasound kidney length >16.5 cm was used.[13] Patients were randomly assigned in a 2:1 ratio to tolvaptan or placebo treatment and was performed centrally by the investigators. All participants, the investigators, care providers, and those assessing outcomes were blinded after treatment assignment.[15] Since REPRISE had fewer young adult subjects than the TEMPO 3:4 study, the TEMPO 3:4 study was used to guide the use of tolvaptan for this age group. Tolvaptan was provided daily in the morning (45 mg) and afternoon (15 mg), and the dosage was adjusted weekly (increase to 60 mg and 30 mg and then to 90 mg and 30 mg, respectively) based on the patient's tolerability. Water intake was encouraged and diuretics were avoided. Treatment with tolvaptan was discontinued if a patient developed end-stage renal disease (ESRD). The detailed study protocol and study results have been published previously.[13,15] Additional information on tolvaptan prescription, dosing, side effects, drug interactions, and monitoring are provided in the Supplementary Table S1.[12,16–18] The institutional review board (IRB) or ethics committee at each site had approved this study, and the study was overseen by a committee of investigators and a representative of Otsuka Pharmaceuticals. This report has been written in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 statements (Supplementary Fig. S1 and Table S2).

Assessment of disease progression

Predicting Renal Outcomes in Patients with ADPKD (PROPKD) score. The PROPKD score is a risk assessment tool developed to predict disease progression in ADPKD patients based on clinical and genetic data. The PROPKD risk score includes hypertension: 2 points; first urologic event: 2 points; *PKD2* mutation: 0 points; non-truncating *PKD1* mutation: 2 points; and truncating *PKD1* mutation: 4 points. The 3 risk categories are defined as low risk (0–3 points), intermediate risk (4–6 points), and high risk (7–9 points) of progression to ESRD.[19] There is great interest in *PKD1* truncating mutation as a potential prognostic biomarker, as patients with these mutations typically have significantly faster progression to ESRD than those with *PKD2* mutations.[16] Since genetic testing is not widely used in ADPKD patients, this scoring system has limited applicability outside of a research setting. PROPKD can only be used in patients aged >35 years or in patients aged <35 years if they are already hypertensive and have experienced urologic complications, such as hematuria.

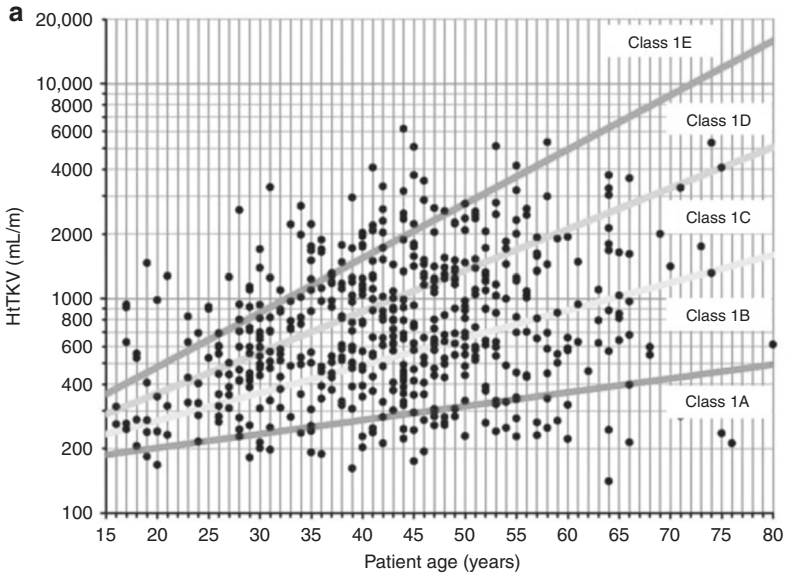
Risk stratification based on height-adjusted TKV (htTKV). While kidney function is of limited value for predicting disease progression early in ADPKD, TKV typically increases from the very early stages of the disease and predicts later changes in eGFR decline. Bhutani and colleagues found that patients with bilateral kidney length of >16.5 cm by ultrasound should be considered at high risk of progression; however, direct measurement of TKV by MRI provides a more accurate assessment.[20] In 2016, the FDA provided a recommendation for the use of TKV as a prognostic enrichment biomarker to select ADPKD patients at high risk of progressive decline in renal function for inclusion in interventional clinical trials.[21]

The prediction tool for ADPKD progression developed from Mayo Clinic Translational PKD Center patients ($n = 590$) by Irazabal and colleagues is based on htTKV and age and was used to predict disease progression.[22] This tool is intended to optimize patient selection for enrollment into clinical trials and defines five risk classes for eGFR decline (1A–1E) in ADPKD. Risk classes 1A–1E encompass "typical" ADPKD presentation, i.e., bilateral and diffuse cyst distribution in which all cysts contribute similarly to TKV. "Atypical" cases (<10%) are excluded, for example, cystic involvement of primarily one kidney or focal disease affecting only a portion of one or both kidneys and sparing the remaining renal tissue. The graph (Fig. 1a) below shows how to classify patients based on htTKV and age in order to estimate the expected annual growth in htTKV, estimated slope of change in eGFR, and overall rate of disease progression for each class (Fig. 1b).[22] Ultimately, these findings demonstrate that a single htTKV measurement is a strong prognostic marker of subsequent eGFR slope.

Although serum uric acid level has not been incorporated into prediction algorithms, data from a large cohort of adult ADPKD patients ($n = 680$) have shown that serum uric acid concentration is positively associated with earlier age of hypertension onset and earlier age of ESRD onset, independently of patient age and level of renal function at the time of assessment.[23]

Renal imaging. Ultrasonography has been shown to be a reliable, non-invasive tool for the diagnosis of ADPKD in children. Specifically, with the degree of resolution available since the 1990s, this method is able to distinguish kidney cysts in nearly 80% of children with known *PKD1* mutations.[24,25] The superior and inferior poles are identified in the longitudinal scan of the kidney, and renal length (*L*) is measured as the longest distance between the poles. The antero-posterior diameter (AP) (thickness) is also measured, and the maximum distance between the anterior and posterior walls at the mid-third of the kidney is taken as an AP diameter. The renal width (*W*) is measured on transverse scan and the maximum transverse diameter is taken at the hilum as the renal width. Kidney volume is calculated using the formula:

$$L \times W \times \mathrm{AP} \times 0.523.$$



b

Class	Expected annual growth in htTKV	Estimated slope of change in eGFR		Rate of disease progression
		Men	Women	
1E	>6.0%	−4.78	−4.58	Rapid
1D	4.5–6.0%	−3.48	−3.29	Rapid
1C	3.0–4.5%	−2.63	−2.43	Rapid
1B	1.5–3.0%	−1.33	−1.13	Intermediate
1A	<1.5%	−0.23	0.03	Slow

Fig. 1 The Mayo classification for prediction of ADPKD progression. a Risk classification of patients with typical ADPKD presentation by htTKV and age. Classes are defined based on the estimated kidney growth rates shown in the adjoining table. **b** Risk classification predicts change in eGFR (in mL/min/1.73 m^2/year) over time. (Reproduced from Irazabal et al.[22] with permission).

The ellipsoid formula was used to calculate TKV from manually measuring the length, width, and depth on ultrasound, MRI, or computed tomography (CT). The two basic ellipsoid equations are as follows:

$$\mathrm{KV} = \pi/6 \times L \times W \times D$$

$$\mathrm{KV} = \pi/12 \times L \times (W + \mathrm{WW})$$

where D = maximum depth, KV = kidney volume, L = maximal longitudinal length, W = maximal width perpendicular to L, and WW = width >W. The value for W is determined perpendicularly to L on the same slice that L is localized on. In addition to W, a greater width than W (WW) was surveyed on the other tilted coronal slice and was used in MRI and reformatted CT images.[22,26]

Outcome measures

The primary outcome was the annual rate of percentage of change in TKV after 3 years for tolvaptan relative to placebo, determined by MRI imaging. Patients with <6-month follow-up were excluded from this outcome analysis due to lack of post-baseline MRI. The secondary outcome was the long-term safety of tolvaptan by assessing the number of patients who had liver toxicity as defined per Hy's law. Hy's law of hepatotoxicity is defined by the combination of aspartate aminotransferase (AST) or alanine aminotransaminase (ALT) levels greater than threefold above the upper limit of the normal (ULN) and serum total bilirubin (BT) more than two times ULN without cholestasis (elevated serum alkaline phosphatase (ALP)). It is vital to exclude any causes other than drug administration to explain elevation in ALT and BT levels. The secondary outcome also included the long-term effects of tolvaptan on urine osmolality (Uosm) in the AYA group and was analyzed for 36 months.

Statistical analysis

For the analysis of the primary endpoint, the rate of percentage of growth per year was calculated by regressing logarithm-transformed kidney volume data against time. The estimated slope was determined from the geometric mean of annualized growth rate from tolvaptan and placebo treatments. The individual slopes were then compared for TKV between the two treatments by fitting the $\log_{10}$-transformed TKV data to a linear mixed-effects Laird–Ware model. The 95% confidence intervals (CIs) and the antilog of the treatment effect derived from the model provided the slope of TKV. Similarly, the P value for heterogeneity comparing the relative effect size in the AYA group (18–24) vs. adult group (25–50) was calculated. The P value comparing the placebo and tolvaptan's effect on Uosm was derived by performing an analysis of covariance with factor of treatments and covariate baseline.

RESULTS

A total of 1445 patients were randomly assigned to either the placebo (484) or the tolvaptan (958) treatment group. Within the AYA subgroup, there were a total of 63 patients (24 in the placebo group and 39 in the tolvaptan group). The demographics and

Table 1. Demographics and patient clinical characteristics at baseline in the AYA group.

Parameter		Tolvaptan[a] ($N = 39$)	Placebo ($N = 24$)	P value
Male sex	No. (%)	14 (44)	12 (50)	0.7951
Age (year)	Mean (SD)	21.51 (1.78)	21.25 (2.23)	0.6071
Caucasian	No. (%)	38 (97)	23 (96)	1.0000
BMI	Mean (SD)	23.22 (6.02)	23.22 (6.02)	0.8064
Blood pressure, mm Hg				
SBP	Mean (SD)	124.4 (13.49)	127.1 (17.47)	0.4980
DBP	Mean (SD)	79.26 (10.34)	80.54 (9.74)	0.6261
Medical history				
Hypercholesterolemia	No. (%)	1 (3)	0	1.0000
Hematuria	No. (%)	12 (31)	7 (29)	1.0000
Kidney pain	No. (%)	18 (46)	11 (46)	1.0000
Kidney stones	No. (%)	3 (8)	5 (21)	0.2409
Urinary tract infection	No. (%)	10 (26)	8 (33)	0.5726
Cholesterol (mmol/L)	Mean (SD)	4.38 (0.70)	4.38 (0.57)	0.9695
Glucose (mmol/L)	Mean (SD)	4.96 (0.52)	4.91(0.80)	0.7628
eGFR (mL/min/1.73 m^2)	Mean (SD)	110.5 (15.61)	120.0 (19.9)	0.0380
htTKV (mL/min)	Median (IQR)	633.5 (476.2, 780.7)	735.3 (526.4, 1017)	0.1425

DBP diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *htTKV* height-adjusted total kidney volume, *SBP* systolic blood pressure.
P values were calculated by Fisher's Exact test for binary characters and by *T* test/Wilcoxon test for continuous variable.
[a]Tolvaptan was titrated to a maximum split dose of 90/30 mg daily as tolerated.

Table 2. Post hoc analysis of tolvaptan treatment effects on TKV rate of growth in the AYA group (1D, 1E subgroup).

Subgroup	Treatment	Rate of % growth per year					Estimated slope	Treatment affect (% improved)	P value
		Mean	Median	SD	Min	Max			
1D, 1E	Placebo ($n = 22$)	6.47	5.76	5.48	−2.03	18.33	6.52		
	Tolvaptan[a] ($n = 28$)	3.82	4.47	3.76	−6.50	13.08	3.76	42.3	0.0452

TKV total kidney volume, *SD* standard deviation.
[a]Tolvaptan was titrated to a maximum split dose of 90/30 mg daily as tolerated.

baseline characteristics in the two treatment groups were well balanced (Table 1). In addition, all patients in the AYA group were classified as 1D and 1E and an analysis between the two treatment groups are shown in Table 2 (one patient in the tolvaptan group classified as 1B). In the adult subgroup, there were a total of 1379 patients with 460 and 919 patients randomly assigned to the placebo and tolvaptan treatment groups, respectively.

Primary outcome

Overall, a total of 1277 patients who had completed the 3-year trial and 6-month follow-up were analyzed. A total of 810 patients were randomly assigned to tolvaptan while 458 patients were assigned to placebo treatment. In the AYAs subgroup, there were a total of 51 patients (22 patients (43%) in the placebo group and 29 patients (57%) in the tolvaptan group). Two patients in the placebo group and 10 patients in the tolvaptan group were excluded from the primary outcome analysis due to a lack of follow-up MRI scans. The adult subgroup consisted of a total of 1226 patients (436 (36%) were in the placebo group while 790 patients (64%) were in the tolvaptan group).

Table 3 shows the percentage of TKV change in the two age groups treated with placebo vs. tolvaptan in the TEMPO 3:4 trials. Over the 3-year period, TKV in the AYAs group treated with tolvaptan increased by 3.8% per year (95% CI, 3.8–5.2) vs. 6.5% per year (95% CI, 4.2–8.6) with placebo. Tolvaptan decreased the rate of growth by 2.7 percentage points per year ($P = 0.0491$) compared to placebo and represents a treatment effect of 41.2%. In the adult group, TKV with tolvaptan increased by 2.7% per year (95% CI, 2.4–3.1) vs. 5.5% per year (95% CI, 5.0–5.9) with the placebo treatment. Similarly, tolvaptan decreased the rate of growth by 2.9% per year ($P < 0.0001$) and had a treatment effect of 49.4% in this population. The treatment effect between the two age groups were compared and was not significant ($P = 0.9093$).

Secondary outcome

A total of 1442 patients, who were randomly assigned to either tolvaptan (958) or placebo (484), were analyzed for ALT, AST, BT, and ALP levels (Table 4). Out of the 63 patients in the AYA subgroup, 24 (38%) were on placebo and 39 (62%) were treated with tolvaptan. In both groups, none of the patients met the criteria for Hy's law of hepatotoxicity. In the adult subgroup, there were a total of 1379 patients (33% (460/1379) in the placebo group and 67% (919/1379) in the tolvaptan group). More patients in the tolvaptan group had ALT levels (4.2% vs. 1.1%, respectively) and AST levels (2.6% vs. 0.9%) >3 times the ULN range compared to the placebo group. However, more patients in the placebo group had higher levels of BT compared to the tolvaptan group (0.7% vs. 0.1%, respectively). Overall, there were no patients in the adult subgroup who satisfied the criteria for Hy's law. In addition, the effect of tolvaptan on Uosm was analyzed in the AYA group. Over 36 months, tolvaptan showed consistent reduction in Uosm by ~300–400 mOsm/kg from baseline (Table 5).

Table 3. Post hoc analysis of tolvaptan treatment effects on TKV growth in young adults and adults in the TEMPO 3:4 clinical trial.

Age subgroup	Treatment	Mean % TKV growth/year	Treatment effect (*P* value)	Treatment effect between age subgroup
18–24	Placebo ($n = 22$)	6.50%	$P = 0.0491$	$P = 0.9093$
	Tolvaptan[a] ($n = 29$)	3.90%		
25–50	Placebo ($n = 436$)	5.60%	$P < 0.0001$	
	Tolvaptan[a] ($n = 790$)	2.70%		

TKV total kidney volume.
[a]Tolvaptan was titrated to a maximum split dose of 90/30 mg daily as tolerated.

Table 4. Post hoc analysis of young adults and adults who experienced abnormalities in ALT, AST, BT, and ALP levels.

Subgroup	Treatment	ALT > 3× ULN (*n*, %)	AST > 3× ULN (*n*, %)	BT > 2× ULN (*n*, %)	AST/ALT > 3× ULN and BT > 2× ULN and ALP < 2× ULN (*n*, %)
18–24 years	Placebo ($n = 24$)	0	0	0	0
	Tolvaptan[a] ($n = 39$)	0	0	0	0
25–50 years	Placebo ($n = 460$)	5, 1.1%	4, 0.9%	3, 0.7%	0
	Tolvaptan[a] ($n = 919$)	39, 4.2%	24, 2.6%	1, 0.1%	0

ALT alanine aminotransaminase, *AST* aspartate aminotransaminase, *ALP* alkaline phosphatase, *BT* serum total bilirubin, *ULN* upper limit of normal.
[a]Tolvaptan was titrated to a maximum split dose of 90/30 mg daily as tolerated.

Table 5. ANCOVA of change in urine osmolality from baseline in the AYA group.

Visit	Treatment (*n*)	Value (mOsm/kg)					Changes from baseline (mOsm/kg)					Dif.	95% CI		*P* value
		Mean	Med.	SD	Min	Max	Mean	Med.	SD	Min	Max		LL	UL	
Baseline	Tolvaptan[a] (35)	600	610	185	138	991.0	–	–	–	–	–	–	–	–	–
	Placebo (26)	668	663	173	274	1024	–	–	–	–	–	–	–	–	–
Week 3	Tolvaptan[a] (34)	208	149	109	92.0	466.0	−393	−406	231.5	−767	247.0	−384	−465	−303	<0.0001
	Placebo (26)	594	568	191	197	1028	−73.6	−77.0	228.5	−640	375.0	–	–	–	–
Month 12	Tolvaptan[a] (18)	265	198	188	99.0	797.0	−331	−361	238.1	−689	234.0	−268	−383	−154	<0.0001
	Placebo (23)	569	555	224	227	931.0	−119	−120	196.0	−427	208.0	–	–	–	–
Month 24	Tolvaptan[a] (18)	242	191	157	74.0	671.0	−355	−391	227.4	−692	61.00	−281	−392	−171	<0.0001
	Placebo (23)	552	553	222	185	877.0	−152	−119	213.5	−545	287.0	–	–	–	–
Month 36	Tolvaptan[a] (28)	233	193	140	90.0	590.0	−360	−405	239.8	−665	60.00	−259	−367	−151	<0.0001
	Placebo (22)	511	498	208	164	918.0	195	−194	209.7	−642	264.0	–	–	–	–

CI confidence interval, *Max* maximum, *Med.* median, *Min* minimum, *LL* lower limit, *SD* standard deviation, *UL* upper limit.
P value was derived from ANCOVA with factor of treatment and covariate baseline.
[a]Tolvaptan was titrated to a maximum split dose of 90/30 mg daily as tolerated.

DISCUSSION

The TEMPO 3:4 trial illustrated that tolvaptan had a beneficial effect on reducing the rate of TKV growth (−2.7 percentage points per year) in patients aged 18–50 years with ADPKD.[13] This information was pertinent toward the approval of tolvaptan in the United States in April 2018, and nephrologists sought to prescribe this medication to AYAs aged 18–24 years. However, owing to the lack of interim analyses to assess use of tolvaptan specifically in AYAs, healthcare providers are currently searching for reliable, evidence-based practice for prescribing tolvaptan to young adults. Therefore, we report a post hoc analysis of the TEMPO 3:4 clinical trial investigating the role of tolvaptan in the management of ADPKD for patients aged 18–24 years.

The results of the analysis of our primary endpoint demonstrated that tolvaptan, compared to placebo, was similarly efficient in reducing TKV change in both the AYA and adult groups. Tolvaptan had a significant treatment effect of tolvaptan in each stratum; 41.2% vs. 49.4% in AYAs and adult patients, respectively ($P < 0.05$). Both groups showed the most significant decrease in TKV during the first year, compared to years 2 and 3. In addition, none of the patients in the AYA stratum met the criteria for Hy's law of hepatotoxicity. In the adult groups, more patients under tolvaptan treatment, in comparison to placebo, had ALT and AST levels greater than three times the ULN range. Discontinuation of treatment spontaneously resolved the elevated liver enzyme levels to baseline. A study by Watkins et al. had different criteria for Hy's law (ALT > 3× ULN and BT > 2× ULN) and reported 3 tolvaptan-treated patients in the TEMPO 3:4 trial who met the criteria. However, even with these criteria, none of the patients in the AYA stratum satisfied Hy's law.[27] Furthermore, tolvaptan decreased the Uosm by approximately 300–400 mOsm/kg over 36 months. This is similar to the study by Devuyst et al., where a reduction by 200–300 mOsm/kg with tolvaptan treatment over 36 months was reported. The authors also suggested that the response was dependent on the baseline eGFR levels, Uosm, and TKV.[28]

This post hoc analysis has several limitations. First, the tolvaptan-treated AYA subgroup contained a relatively smaller subject size ($n = 51$) in comparison to the adult group, and as a result, it cannot be firmly inferred that tolvaptan has beneficial effect in this subgroup. This analysis also did not include the effect of tolvaptan on eGFR decline for the AYA subgroup. This information would have been greatly beneficial in elucidating whether tolvaptan was able to recover renal function in this age range. However, there is currently a phase 2b clinical trial underway to assess the safety of treatment with tolvaptan in children and adolescents (aged 12–17 years), and those results will not directly reflect on tolvaptan's effect in the AYA stratum.[29]

In summary, this post hoc analysis of the TEMPO 3:4 trials suggest that tolvaptan was able to slow the increase in TKV in AYAs with high risk of rapidly progressive ADPKD. In addition, there was no risk of potential liver injury in the AYA group treated with tolvaptan, as none of the patients displayed abnormal liver enzyme levels or met Hy's law of hepatotoxicity. Therefore, with appropriate patient selection and management, tolvaptan can provide effective and acceptably safe treatment in AYAs with ADPKD. Future studies with larger patient population are needed to further illustrate the efficacy and safety of tolvaptan in patients aged 18–24 years.

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AUTHOR CONTRIBUTIONS

R.R., M.E.D., and T.K. contributed to the conception and design of this study. R.R., R.C., and T.K. were involved in the data analysis and interpretation of the data. R.R., R.C., and M.E.D. drafted the article and revised it critically for important intellectual content. All authors have approved the final version of this manuscript.

ADDITIONAL INFORMATION

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Patient consent: Informed consent was obtained from all patients, and this study was approved by the institutional IRB.

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