REVIEW

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Recent updates in therapeutic approach using tolvaptan for autosomal dominant polycystic kidney disease

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As a genetic disease, there has been a long-standing effort to identify therapeutic options for autosomal dominant polycystic kidney disease (ADPKD). Following the development of tolvaptan, a vasopressin 2 receptor antagonist, the treatment strategy for ADPKD patients with rapid disease progression has been changed with a disease-targeted approach. Tolvaptan showed significant efficacy in preserving kidney function and reducing the total kidney volume (TKV) growth rate. These effects were especially pronounced in patients with more severe clinical phenotypes, such as higher TKV and rapidly declining kidney function. Despite the therapeutic effects of tolvaptan, aquaretic symptoms are unavoidable side effects related to the mechanism of the drug and are also directly related to the quality of life. A shared decision-making process could be a valuable strategy for reducing the incidence of side effects and improving medication adherence. Herein, we aimed to review overall clinical trials for applying tolvaptan and suggest important factors during the shared decision-making process.

Keywords: Polycystic kidney, autosomal dominant; Tolvaptan; Decision making, shared

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the leading cause of end-stage kidney disease (ESKD) among inherited kidney diseases [1,2]. Despite autosomal dominant traits, the diagnosis of ADPKD tends to be delayed due to late-onset clinical manifestations. However, timely recognition and identification of the disease are essential, as early diagnosis and intervention by disease-modifying drug such as tolvaptan can slow disease progression.

Cyst formation is the main pathognomonic sign of multisystemic disease. Although several pathways are implicated in the pathogenesis of PKD, dysfunction of primary cilia represented by ciliopathy, plays a critical role. Polycystin-1 and polycystin-2 are located in the primary cilia and have diverse functions, such as cellular antenna, chemosensory, and chemosecretory roles. In addition, the polycystin complex is the most upstream component that mediates the translation of extracellular mechanical signals to intracellular biochemical downstream signals [3]. Dysregulation of cyclic AMP (cAMP) signaling is another key factor in intracellular renal epithelial signaling in ADPKD [4]. As a result of the dysfunction of polycystin-1 or polycystin-2 at the primary cilia, complex responses to decreased calcium influx, activated protein kinase A, and increased cAMP signaling may induce cellular proliferation, cellular adhesion, fluid secretion, and cystogenesis [5].

Arginine vasopressin (AVP) plays a pivotal role in maintaining fluid homeostasis in the body [6,7]. The level of circulating AVP is increased in patients with ADPKD, and the concentration of copeptin, a surrogate marker of vasopressin, is associated with disease severity [5,8]. Moreover, pharmacological inhibition of cAMP signaling using tolvaptan, a selective vasopressin 2 receptor (V2R) antagonist, has been reported to reduce fluid secretion, cell proliferation, and cyst growth rate in human ADPKD cyst epithelial cells [9,10]. Based on

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these positive results in preclinical research, clinical trials following a stepwise approach to evaluate the safety and efficacy of tolvaptan were introduced to patients with ADPKD [11-13]. Following approval in Japan in March 2014, Canada and European Union in February 2015, and South Korea in December 2015, tolvaptan was approved by the U. S. Food and Drug Administration as the first therapeutic agent for adult patients with ADPKD in April 2018 (Fig. 1). Herein, we aimed to provide a comprehensive overview of clinical trials for the application of tolvaptan and to propose clinically important factors for the shared decision-making process.

BENEFICIAL EFFECTS OF TOLVAPTAN

Impact of tolvaptan on total kidney volume (TKV)

TKV is a marker representing renal cyst development and expansion; thus, measuring TKV provides the course of ADPKD progression and severity [14]. In addition, the assessment of age and height-adjusted TKV could support the classification of kidney growth curves. It is usually divided into five categories from 1A to 1E based on the mayo classification, and patients with 1C-1E are generally regarded as a rapid progressors [15-17]. In this regard, the Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO) 3:4 study, a landmark trial of tolvaptan, aimed to evaluate the efficacy of tolvaptan with the annual rate of change in TKV and estimated glomerular filtration rate (eGFR) slope. Tolvaptan demonstrated significant efficacy in the TEMPO 3:4 trial, reducing the annual rate of change in TKV by 2.8% per year in the tolvaptan group compared to the 5.5% per year in the placebo group [12].

The effect of tolvaptan on TKV was maintained irrespective of sex, age, hypertension, eGFR, and baseline TKV (Table 1). In addition, the decline in TKV growth rate was most significant in the 1st year of tolvaptan administration [18]. The extension trial of TEMPO 3:4 also showed a prominent de-

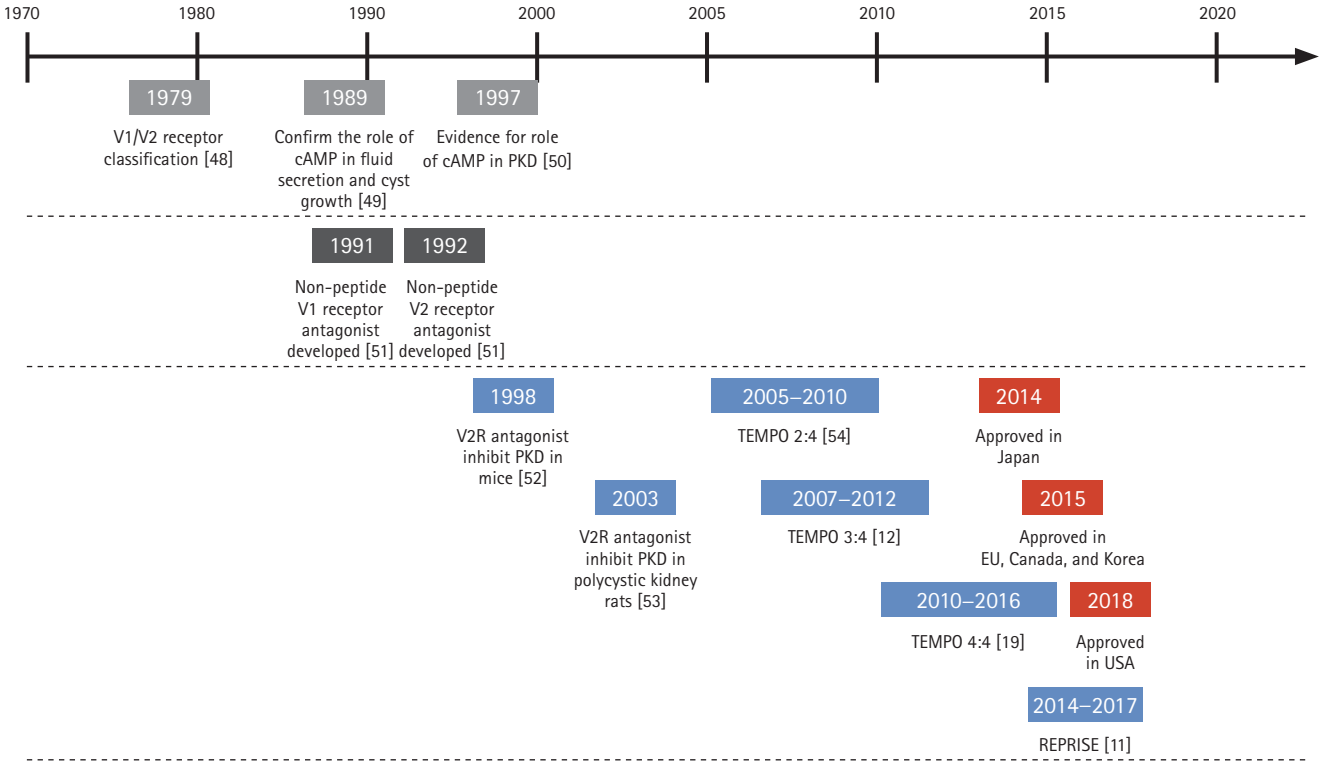

Figure 1. History of tolvaptan development from bench to clinical application. The first row shows the discovery of vasopressin V1/V2 receptors and the role of cyclic adenosine monophosphate in the development of polycystic kidney disease [57-59]. The second row shows the development of the first nonpeptide vasopressin 1 receptor (V1R) and V2R antagonists [60]. The third row and below represent the overall trials from the experimental to a clinical trial for the application of V2R antagonists and the approval status worldwide [11,12,19,61-63]. cAMP, cyclic AMP; PKD, polycystic kidney disease; TEMPO, Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes; REPRISE, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD.

Table 1. Efficacy of tolvaptan based on clinical trials

	TEMPO 3:4	TEMPO 4:4	REPRISE
Total	1,445	871	1,370
Inclusion criteria	18–50 years, eGFR ≥ 60 (CG calculate) TKV ≥ 750 mL by MRI	Patients completing TEMPO 3:4	18–55 years & eGFR 25–65 56–65 years & eGFR 25–44
Periods	36 months	Additional 24 months	36 months
Primary endpoint	Annual change in TKV 2.8%/year vs. 5.5%/year	TKV change from TEMPO 3:4 baseline 29.9% in early- vs. 31.6% in delayed-treated subjects (p = 0.38)	1-year eGFR changes -2.34 vs. -3.61 (difference, 1.27; p < 0.0001)
Secondary endpoint	Clinical events • Hypertension (p = 0.42) • Albuminuria (p = 0.74) • Renal pain (HR, 0.64; p = 0.01) • Renal function (HR, 0.39; p < 0.001)	eGFR & TKV (compared between early- and delayed-treated subjects) • eGFR changes from TEMPO 3:4 baseline (difference in eGFR decline: 3.15 mL/min/1.73 m^2) • TKV slope in TEMPO 4:4 (difference, 1.01 mL; p = 0.046) • eGFR slope in TEMPO 4:4 (difference, -0.11; p = 0.73)	Annualized eGFR slope -3.16 vs. -4.17 (difference, 1.011; p < 0.0001)

TEMPO, Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes; REPRISE, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD; eGFR, estimated glomerular filtration rates; CG, Cockcroft-Gault; TKV, total kidney volume; MRI, magnetic resonance imaging; HR, hazard ratio.

crease in the rate of change in TKV in the 1st year in patients newly started on tolvaptan, irrespective of whether treatment was initiated early or delayed [19]. In the subgroup analysis, the effect of tolvaptan on TKV was prominent in subjects with more severe clinical phenotypes, such as 1C-1E of the Mayo classification and with genotypes including PKD1-truncating mutation. The treatment difference for TKV between early and delayed treatment was 4.15% at month 24 in TEMPO 4:4. This difference was maintained in subjects with more severe clinical phenotypes. Considering the sustained benefit of early treatment to reduce the rate of TKV increase, early initiation of tolvaptan is recommended for patients with ADPKD, especially those with more severe clinical phenotypes or truncating mutations in PKD1.

Preserving kidney function

Tolvaptan significantly reduced the risk of worsening kidney function [12]. In TEMPO 3:4 trial, the annual rate of change in kidney function was -2.61 and -3.81 mL/min/1.73 m^2 in patients with and without tolvaptan, respectively. The attenuation of kidney function decline was similar in the Japanese subpopulation [20]. This effect was maintained irrespective of sex or baseline kidney function. In addition, the difference in eGFR slope between the tolvaptan and placebo group was maintained in patients with age ≥ 35 years, presence of hypertension, and TKV ≥ 1,500 mL [12]. After including more advanced chronic kidney disease (CKD) patients with eGFR 25–60 mL/min/1.73 m^2, annual eGFR decline was 1.27 mL/min/1.73 m^2 less in patients with tolvaptan than without tolvaptan [11]. The attenuation of kidney function decline was maintained in patients with baseline eGFR ≥ 45 mL/min/1.73 m^2 (1.23, p < 0.001), and eGFR < 45 mL/min/1.73 m^2 (1.34, p < 0.001). Moreover, the effect of delayed eGFR decline was maintained in subjects with eGFR 15–24 mL/min/1.73 m^2 [21].

In the long-term extension trial of TEMPO 4:4, the difference in the effect of tolvaptan in slowing kidney function decline was maintained after 24 months between the early and delayed treatment groups. However, eGFR slopes were similar in the early- and delayed-treatment groups (-3.26 vs. -3.14 mL/min/1.73 m^2 per year; treatment difference, -0.11; p = 0.73) [11]. In the subgroup analysis, the effect of preserving kidney function was prominent in patients with more severe clinical phenotypes, similar to changes in TKV. Although there have been no reports considering ESKD as an outcome, the positive effect of preserving kidney function has been maintained in most studies [22,23]. Extrapolations from the results of the TEMPO 3:4 suggested that

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tolvaptan may delay the onset of ESKD by 7.3, 4.4, 2.9, and 1.5 years according to the baseline eGFR 90, 60, 45, and 30 mL/min/1.73 m^2, respectively [24]. The extrapolation result from Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial showed a similar pattern; 6.8, 4.5, and 2.3 years in baseline eGFR of 60, 45, and 30 mL/min/1.73 m^2, respectively [24]. These modeling to predict ESKD suggested that tolvaptan could delay the mean age of ESKD, and the estimated time lag to delay ESKD was greatest among patients with more preserved kidney function [25].

Other beneficial effects

Kidney pain, a common complication in patients with ADPKD, is often reported early in the disease course [26]. Acute kidney pain events are related to urologic complications such as urinary tract infections, kidney stones, and cyst bleeding and rupture. Tolvaptan significantly reduced the incidence of kidney pain events compared to the placebo, with a risk reduction of 36%. The relative risk factors for kidney pain were a history of kidney stones, hematuria, or female sex, and it was not different according to the use of tolvaptan [27].

The prevalence of kidney stones was reported up to 36% in patients with ADPKD, and it showed higher a frequency of uric acid stones compared to general populations [28]. A higher prevalence of kidney stones could be related to lower urine volume, lower urine pH with low urine ammonium, hyperuricosuria, and hyperoxaluria. As an anatomical factor, larger kidney volume is an independent risk factor for kidney stones [29]. Although tolvaptan administration did not change urinary solute excretions; it may reduce urine osmolarity and increase urine volume. In addition, urinary super-saturation for calcium oxalate and calcium phosphate, the main components of urinary stones, significantly decreased after using tolvaptan in a pilot study [30]. Another prospective study also showed similar results for reducing lithogenic risk profile, including supersaturation for calcium oxalate, brushite, and uric acid in patients with tolvaptan. Despite these beneficial effects of tolvaptan on the lithogenic risk profile, there was a lack of data on the association between preexisting stone and tolvaptan.

HEEDFUL FACTORS FOR TOLVAPTAN USE

Aquaretic symptoms

Aquaretic symptoms, including thirst, polydipsia, polyuria, nocturia, and pollakiuria, are the most common side effects of tolvaptan [11,12]. These symptoms were detected as a significant side effect of tolvaptan in most trials, and the incidence was variable [31]. These symptoms are unavoidable responses associated with the mechanism of V2R blockade. Aquaretic symptoms following water diuresis induce discomfort with frequent urination, sleep disturbance, and fatigue. This was the main reason for discontinuing the drug in the TEMPO 3:4 trial, and thirst was the most common adverse event experienced by more than half of the patients [12]. Among the patients with aquaretic adverse events, approximately 10% of patients discontinued tolvaptan. These patients were younger and had a higher baseline eGFR and urine osmolarity than those who continued tolvaptan [32].

Aquaretic symptoms were mostly tolerated within 4 months after drug initiation [32,33]. Based on the long-term open-label extension trial for patients who completed TEMPO 3:4, TEMPO 4:4, or REPRISE, representative symptoms such as thirst, polyuria, and nocturia were reduced following more prolonged exposure to the drug [34]. Osmolar excretion is the primary determinant of urine volume, and lowering dietary sodium intake helps reduce urine volume by reducing osmotic diuresis with active solutes [35-38]. Although the concomitant use of thiazides to reduce urine volume was considered based on a report on nephrogenic diabetes insipidus, there is insufficient evidence to support this hypothesis [39,40].

Tolvaptan-induced liver injury

The association between tolvaptan use and hepatic adverse events has been reported with the idiosyncratic and reversible elevation of blood aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The prevalence was reported to be < 2% to 10.9% of patients in clinical trials, and severe and potentially life-threatening liver injury is rare and reversible [31,41]. Nevertheless, there was a case that required liver transplantation due to fulminant hepatic failure after using tolvaptan [42]. Thus, liver function should be monitored regularly.

The prevalence of hepatotoxicity incrementally decreases with exposure to tolvaptan [11,34]. Time-to-event analysis of the TEMPO trials showed that hepatotoxic events developed

3 to 18 months after commencing tolvaptan [41]. Thus, guidelines recommend monitoring liver function monthly for 18 months, thereafter every 3 months after initiation of tolvaptan [24,43,44]. It is also necessary to consider drug-drug interactions that increase tolvaptan exposure, such as cytochrome CYP3A4 inhibitors, organic anion transporter 3 substrates, and breast cancer resistance protein transporter substrates [45].

Hyperuricemia

Tolvaptan increased serum uric acid levels owing to decreased renal clearance. Patients who received tolvaptan more frequently experienced hyperuricemia (3.9% vs. 1.9%) and gout (2.9% vs. 1.4%) compared to the placebo group [12]. The prevalence of hyperuricemia incrementally increased according to the CKD stage, irrespective of tolvaptan treatment (tolvaptan vs. placebo: 20.7% vs. 12.9% in CKD stage 1, 38.7% vs. 24.7% in CKD stage 2, 71.8% vs. 49.4% in CKD stage 3) [46]. Considering the risk of hyperuricemia and gout with CKD progression [47,48], proper monitoring and intervention with urate-lowering agents are required in patients receiving tolvaptan, even if there are no reports on discontinuation of tolvaptan due to hyperuricemia.

CLINICAL APPLICATIONS OF TOLVAPTAN

Patient selection based on the assessment of the risk of disease progression

ADPKD has a heterogeneous clinical phenotype with a wide range of cystic burdens. The only disease-modifying drug, tolvaptan, showed a significant effect, particularly in subjects classified as rapid progressors. Therefore, the initial search for a suitable candidate for tolvaptan is important. The assessment strategy for identifying the risk of rapid progression differed according to consensus, but the overall points were similar (Table 2). The primary determinant was kidney volume, defined as TKV of 750 mL or Mayo classification 1C-1E. The recently updated European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) guidelines state that additional evidence for rapid disease progression is required to access a rapidly progressing disease in patients with Mayo class 1C [44]. Another significant determinant was kidney function, represented by the eGFR slope. Rapidly decreased kidney function was usually defined as an eGFR slope of 2.5 mL/min per year over 5 years.

Considering that the effect of preserving kidney function decreased steadily with the lower baseline eGFR, the lower limit to start tolvaptan was about 30 mL/min/1.73 m^2. However, it was lowered to 25 mL/min/1.73 m^2 in the recently updated ERA-EDTA guidelines based on the results from the REPRISE trial [11]. Furthermore, the efficacy of tolvaptan in patients with advanced-stage CKD has been updated [49,50]. Age is one of the factors that should be considered when tolvaptan is used as a therapeutic option. Most clinical trials were conducted in patients younger than 55 or 65; overall, guidelines suggest an upper limit of 55 or 65 years. The NICE commentary did not state the upper limit of age, but they suggested that patients older than 50 years with stage 3 CKD could be classified into a better prognostic group; thus, additive factors would be necessary to use tolvaptan [51]. Contrary to the European and USA guidelines, the Japanese guidelines do not indicate the upper limit of age [52,53]. Because of aquaretic symptoms associated with tolvaptan, self-care performance status should be considered before initiating tolvaptan in older patients.

Based on these critical factors, the use of tolvaptan should be considered more positively in young patients with rapidly progressive clinical factors such as Mayo class 1D-1E or rapidly declining eGFR.

Shared decision-making

Tolvaptan showed a positive effect on preserving kidney function, with a delayed increase in TKV in patients with ADPKD. These effects are more prominent in patients with a rapid disease progression. However, aquaretic side effects are unavoidable symptoms following tolvaptan use and are closely associated with quality of life. Therefore, a shared decision-making process based on a detailed discussion of the use of tolvaptan and the risks and benefits of the medication, including its unpleasant effects on lifestyle, is essential.

A shared decision-making process could be started from a hospital visit with a willingness to treat ADPKD. First, physicians should evaluate the disease status based on laboratory tests, image tests, and genetic evaluations. After the assess the objective medical factors, the physician selectively provides treatment options including tolvaptan, based on the collected information. In patients requiring tolvaptan, physicians should provide information on benefits and side

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Table 2. Determinants for rapid progression according to the published guidelines

	Date	Age, yr	eGFR	TKV	Mayo classification	eGFR change	TKV change	Genetics	Kidney length by ultrasound
US-practical guide	2018	18–55	≥ 25	NA	1C-1E	NA	NA	NA	NA
Canadian expert consensus	2018	18–65	25–65	> 750 (if 18–50 years and eGFR > 45)	1D-1E, 1C (if age < 50 years + eGFR decline > 2.5/year or TKV growth > 5%/year)	>2.5 mL/min/year	> 5%/year	NA	> 16.5 cm, each kidney
PBS Australia	2018	≥ 18	30–89	NA	NA	> 5 mL/min in 1 year or > 2.5 mL/min/year over 5 years	NA	NA	NA
ERA-EDTA	2016	18–50	≥ 30	NA	1C-1E	> 5 mL/min in 1 year or > 2.5 mL/min/year over 5 years	> 5%/year	Truncated PKD1 + early symptoms or PROPKD > 6	> 16.5 cm by age 45 years
ERA-EDTA	2021	18–55	≥ 25	NA	1D-1E, 1C (+ additional evidence for rapid progression)	≥ 3 mL/min/year over ≥ 4 years	NA	Truncated PKD1 or PROPKD > 6	> 16.5 cm by age 45 years
NICE	2016	≥ 18	30–89	> 750	1C-1E	>5 mL/min in 1 year or > 2.5 mL/min/year over 5 years	> 5%/year	PROPKD > 6	NA
Japan's guideline	2014	No limit	≥ 60	≥ 750	NA	NA	NA	NA	NA

eGFR, estimated glomerular filtration rates; TKV, total kidney volume; US, ultrasonography; NA, not applicable; PBS, pharmaceutical benefits scheme; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; PKD, polycystic kidney disease; PROPKD, Predicting Renal Outcome in Polycystic Kidney Disease; NICE, National Institute for Health Care and Excellence.

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effects before deciding to use tolvaptan. During this process, it also needs to consider the personalized factors such as job, household income, family, insurance, and lifestyle of the patient. If a patient decides to take tolvaptan, the physician should provide additional dietary counseling to reduce the daily osmolar load by reducing sodium and protein intake. In addition, it is necessary to provide a way to modify the schedule for tolvaptan in particular conditions, such as acute illness or travel where there is difficulty drinking water. These overall steps could improve drug adherence and the satisfaction of patients. Even if a patient decides not to take tolvaptan, a physician could provide general management including blood pressure, diet, and lipid control.

Monitoring

Two aspects should be monitored after commencing tolvaptan treatment: efficacy and side effects. Above all, liver function tests are warranted monthly until 18 months after initiating treatment, and thereafter, should be monitored every 3 months. Tolvaptan should not be administered to patients with increased AST, ALT, or bilirubin levels > 2 times the upper limit of normal (ULN) or > 2 times the baseline. In these cases, liver function tests should be repeated within 48–72 hours. In addition, other factors related to increasing liver function such as acute hepatitis, and concomitant hepatotoxic agents should be evaluated. After returning to the normal range, tolvaptan could be resumed; however, tolvaptan should be permanently discontinued in patients without evidence for other offending causes except for tolvaptan and with follow laboratory results; 1) AST or ALT > 3 times the ULN and bilirubin > 2 times the ULN, 2) AST or ALT > 5 times the ULN over 2 weeks, or 3) AST or ALT > 8 times the ULN [54].

Reduced urine osmolarity is a direct response to tolvaptan application via V2R blockade. Splitting doses of tolvaptan provided sustained reduced urine osmolarity, and these responses were more significant at higher doses [40]. Based on the pharmacokinetic study, the minimum effective dose of tolvaptan was suggested as 30/15 divided doses and maintaining urine osmolarity < 280 mOsm/kg was regarded as a target value in patients taking tolvaptan. However, it cannot represent efficacy; it can only be used as a valuable marker for monitoring medication adherence [55].

Treatment efficacy is usually monitored by eGFR decline, TKV growth rate, and quality of life. A single measurement of eGFR could contain diverse confounding factors with individual fluctuations; hence, kidney function should be monitored using the eGFR slope with repeated checks at scheduled intervals. Kidney function can be compared to the expected value provided by the Mayo Clinic, but its sensitivity and validity have not yet been established. Therefore, caution is required when interpreting and applying it clinically, especially in patients with advanced-stage CKD. As the main target of tolvaptan treatment, it is necessary to monitor the TKV. However, there are several limitations in monitoring TKV, especially in a clinical setting. The method of measuring TKV varies according to the image type and the reading specialist. In addition, there is a common lack of serial images before and after tolvaptan use. Therefore, TKV monitoring is not recommended for individual patients [44,56].

Issues that need to be solved

Large clinical trials have suggested the beneficial effect of tolvaptan for preserving kidney function with reducing the rate of TKV increase. Nevertheless, no report revealed the impact on hard outcomes such as ESKD and all-cause mortality. Although extrapolation data from TEMPO 3:4 and the REPRISE trial suggested prolonging the time spent to ESKD, these results should be considered prediction values, not actual data. In this regard, more research with longer follow-up is still necessary.

Recommendation for tolvaptan has been focused on the patient with rapid progressive clinical phenotype. Rapid progressor is usually confirmed based on the Mayo classification, 1C-1E. In contrast to the patients with 1D-1E, it is controversial whether patients with 1C are rapid progressors or not. Further evaluation for age, eGFR decline, and genetic variants should be considered to reveal rapid progressor in patients with 1C, especially close to 1B.

There were different guidelines for the upper limit of age to use tolvaptan. Based on the clinical trial, which showed the data only for ages < 55 or 65 years, most guidelines suggest it as an upper limit. However, considering the recent extension of life expectancy and changes to an aging society, this age limit may deprive many patients of treatment opportunities. In addition, although the risk of adverse effects such as aquaretic symptoms should be considered, a more in-depth shared decision-making process may be necessary to consider particular physical conditions, including underlying comorbidities.

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CONCLUSION

Tolvaptan could reduce the TKV growth rate and preserve kidney function in patients with ADPKD, especially those with rapidly progressive disease. Despite these beneficial effects, patients may experience diverse side effects, including aquaretic symptoms, hepatic dysfunction, and hyperuricemia. In-depth discussions before initiating tolvaptan could support safer and more sustainable clinical applications. Additional evidence-based research on the safety and efficacy of tolvaptan is required to extend the clinical applications of this novel, effective medication.

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