Review article

Kosin Medical Journal 2023;38(2):87-97
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.23.125

KMJ
KOSIN MEDICAL JOURNAL

Are you ready to accompany autosomal dominant polycystic kidney disease patients in their treatment journey? Real practice for selecting rapid progressors and treatment with tolvaptan

Yeonsoon Jung[1], Yun Kyu Oh[2]

[1]*Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea*
[2]*Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea*

Tolvaptan treatment is costly, often accompanied by aquaresis-related adverse events, and requires careful monitoring by medical staff due to the possibility of hepatotoxicity. Nevertheless, it is the only disease-modifying drug to date that has been shown to successfully delay renal replacement therapy. For more patients to receive proper treatment, medical doctors, the rest of the medical team, and the patient must all work together. This paper reviews parameters that can help identify rapid autosomal dominant polycystic kidney disease progressors, who are the target of tolvaptan therapy. It is expected that these parameters will help nephrologists learn practical prescription methods and identify patients who can benefit from tolvaptan treatment. Although several strategies can be used to find rapid progressors, the present review focuses on a practical method to identify rapid progressors according to the presence or absence of evidence and the factors associated with rapid progression based on the Mayo image classification.

Keywords: Patient selection; Polycystic kidney, autosomal dominant; Tolvaptan

Introduction

In the 1980s and 1990s, the focus of treatment was limited to managing the complications of autosomal dominant polycystic kidney disease (ADPKD), such as hypertension and urinary tract infections. The standard approach for managing ADPKD involved using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to control blood pressure [1,2]. Recent years have seen significant advancements in the understanding of the molecular mechanisms underlying ADPKD, which have led to the development of targeted therapies. Tolvaptan, a selective vasopressin 2 receptor (V2R) antagonist, has been tested in two large, randomized, clinical trials in ADPKD: the TEMPO study published in 2012 and the REPRISE study published in 2017. In the TEMPO 3:4 trial [3], tolvaptan decreased kidney growth by about 49% and slowed the rate of decline in kidney function by about 1.2 mL/min/yr. Meanwhile, in the REPRISE [4], estimated glomerular filtration rate (eGFR) decreased 35% less in the tolvaptan group than in the placebo group in patients with advanced ADPKD (eGFR 25–65 mL/min/1.73 m^2) over 1 year. Tolvap-

Received: May 15, 2023; **Revised:** June 14, 2023; **Accepted:** June 16, 2023
Corresponding Author: Yun Kyu Oh, MD, PhD
Department of Internal Medicine, SMG-SNU Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea
Tel: +82-2-870-2219 Fax: +82-2-870-3863 E-mail: yoonkyu@snu.ac.kr

tan was approved by the U.S. Food and Drug Administration in 2018 as the first medication to slow the progression of ADPKD in adults with a rapidly progressing disease. It has been shown to reduce the rate of kidney growth and preserve kidney function.

Although tolvaptan is a promising treatment option for ADPKD, there are several obstacles restricting the widespread use of tolvaptan in the treatment of ADPKD patients [5]. One of the most significant drawbacks of tolvaptan is its potential for causing liver injury. In clinical trials, a small percentage of patients taking tolvaptan experienced elevations in liver enzymes, which can indicate liver damage. Another potential disadvantage of tolvaptan is its cost. Tolvaptan is an expensive medication, and its long-term cost-effectiveness has not yet been established. This may limit its availability to patients who cannot afford it or who do not have access to health insurance that covers the cost of the medication. Tolvaptan may also cause aquaresis-related adverse effects such as thirst, increased urination, dry mouth, and dehydration. Patients taking tolvaptan should be advised to drink sufficient fluids to prevent dehydration. Finally, tolvaptan is not appropriate for all patients with ADPKD. It is approved for use in adults with rapidly progressive ADPKD, but its safety and efficacy in other patient populations—such as children, pregnant women, and those with severe liver or kidney disease—has yet to be established [6,7]. It is also difficult to find patients with indications for treatment because there are no simplified and effective guidelines. The methods of selecting treatment targets vary from guideline to guideline. These are the reasons why doctors do not readily use tolvaptan. The risks and benefits of tolvaptan should be carefully weighed before it is prescribed.

This paper will review parameters that can help predict rapid progression to find a rapid ADPKD progressor that can serve as the target of tolvaptan therapy. It is also expected that these parameters will help nephrologists learn practical prescription methods and find treatment patients who can benefit from tolvaptan treatment.

How can rapidly progressive polycystic kidney disease patients be predicted?

ADPKD patients show various clinical courses related to renal function decline, but they are stratified as showing slow or rapid progression. The current treatment goal is to select patients with rapid renal function decline among all ADPKD patients (rapid ADPKD progressor) and administer tolvaptan to slow the rate of renal function decline. The first step in achieving this goal is to know the definition of rapid ADPKD progression. Rapid ADPKD progression may be defined as reaching kidney failure at a relatively young age; the cutoff value of young age has not yet been clearly determined and will be higher in patients who want to remain productive and active in society. In an analysis from the Mayo polycystic kidney disease (PKD) clinical database of 1,076 patients with ADPKD who reached kidney failure, 75% of patients reached kidney failure by the age of 62 years old [8]. According to data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) registry, the mean age of dialysis treatment was 58 years old [9], and the Genkyst cohort also reports the median age of renal failure as 61.7 years old [10]. Therefore, it is reasonable to define rapid ADPKD progression as reaching renal failure in the late fifth to early sixth decade.

To find a rapid progressor among all ADPKD patients and use tolvaptan—a disease-modifying drug that can prolong kidney life—rapid progression must be predicted. It is not easy to predict who will develop kidney failure at an early age, and various methods are currently used to predict this. All of these methods have their own strengths and limitations, and their focuses can largely be divided into the risk of rapid progression, evidence of rapid progression, and factors that can affect rapid progression. Risk is the primary method for predicting rapid ADPKD progression before renal function decline occurs. Evidence has a limitation in that renal function decline already exists at the time that any evidence is found, but it can help predict rapid ADPKD progression relatively early if detected during continuous frequent follow-up. There are no known factors that can conclusively determine the effect on rapid progression, but there are various markers that can serve important roles in determining treatment as factors suggesting rapid ADPKD progression. In finding a rapid progressor, the predictive power is in the order of risk, evidence, and factor. Using these markers, different assessment strategies for detecting rapid progression have been created and used to determine treatment in various countries [8]. These various methods can be classified into three types and are described in Table 1. The specific methods used to determine actual treat-

Table 1. Patient selection guideline based on risk, evidence, and factors

Risk	Evidence	Factors
Primary predictors of rapid progression	Markers that prove rapid progression	Markers that are suggestive, not conclusive, of rapid progression
Measurement of TKV: Ellipsoid method Stereology Planimetry	Historical eGFR data TKV growth rate (%/yr)	Genetic test Clinical parameters
Mayo imaging class 1C, 1D, 1E	eGFR decline ≥3 mL/min/1.73m^2 per yr (≥5 times values over 4 yr) eGFR indexed for age: 40–44 yr, eGFR <90 mL/min/1.73 m^2 45–49 yr, eGFR <75 mL/min/1.73 m^2 50–55 yr, eGFR <60 mL/min/1.73 m^2 TKV growth ≥5% per yr (3 measurements at least 6 mo apart)	*PKD1* mutation First urologic event before age 35 yr Hypertension before age 35 yr Family history of first-degree relative with kidney failure before age 55 yr

The various methods of defining risk of rapid progression in autosomal dominant polycystic kidney disease (ADPKD) are classified as being based on risk, evidence, and factors of rapid ADPKD progression.
TKV, total kidney volume; eGFR, estimated glomerular filtration rate.

ment using these three kinds of markers will be described in the patient selection section of this paper, which will be presented later.

1. Risk prediction

The most important consideration in selecting a target for treatment with tolvaptan is to predict the risk of rapid progression of ADPKD. The best predictor of rapid progression is Mayo imaging classification (MIC). This prediction model can classify patients with typical ADPKD into classes 1A through 1E according to height-adjusted total kidney volume (TKV) for age [11]. MIC was based on a study of Caucasians, but it has also been shown to be effective for defining rapid progressors for candidates for tolvaptan treatment among Korean ADPKD patients [12]. It is a very easy and accurate method that can predict renal prognosis based on a single TKV measurement. Patients with more advanced classes of ADPKD may be at higher risk for these complications. It is known that, among MIC classes, patients with 1C to 1E have a high risk of rapid progression, and these patients are the primary targets for active treatment. Class E has been shown to have an annual TKV growth rate of more than 6% and an eGFR slope of –3.25 mL/min/1.73 m^2 per year at an early age in their 20s, while class D is known to have an annual TKV growth rate of 4.5% to 6% and an eGFR slope of –3.37 mL/min/1.73 m^2 per year at an early age in their 30s [11,13]. Therefore, patients in classes D and E are the most active targets for treatment as rapid progressors. Class 1C includes both rapidly and slowly progressive disease with respect to the rate of eGFR decline. In the case of class C, there are countries that use rapid progression as the standard for treatment when there are other risk factors [14,15].

Because MIC should be used as a primary method for risk prediction in routine clinical care, nephrologists must be able to diagnose the typical type of ADPKD and understand how TKV should be measured. The ellipsoid method, stereology, and planimetry method are used for TKV measurement. Nephrologists should ensure that they are familiar with the measurement of TKV using the ellipsoid method, because selection for the treatment of tolvaptan can be achieved in a clinical setting through measurement using the ellipsoid method. The ellipsoid method can be used to calculate TKV from manual measurements of length, width, and depth from magnetic resonance imaging or computed tomography scans. In current clinical practice, the classification of the typical ADPKD calculator web-based application provided by the Mayo PKD Center is used as a method for determining MIC in ADPKD patients. The ellipsoid formula provided by this application is $\pi/6 \times L \times W \times D$, where D=maximum depth; L=mean maximal sagittal and coronal longitudinal length; and W=maximal width (Fig 1A) [11]. In most patients, the TKV value measured using the ellipsoid method is sufficient to determine

tolvaptan treatment. However, it is important for a very accurate measurement method such as the stereology or planimetry method to be used, particularly in cases of B/C borderline in a young patient and TKV measurement excluding prominent exophytic renal cyst [8]. An expanded imaging classification can recalculate TKVs by excluding prominent exophytic cysts in class 1 patients with prominent exophytic cysts, thus leading to improved predictions for developing chronic kidney disease (CKD) stage 3 and eGFR trajectories (Fig. 1C, 1D) [16]. Excluding the exophytic renal cyst, when TKV was measured, 20.9% (10/43) of the patients changed from class 1D and 1C to class 1B, thus demonstrating the importance of using accurate measurement methods. Planimetry is considered to be the golden standard method for the measurement of TKV, and it involves having an image analyst manually trace the kidney borders in images [17,18]. Stereology requires the choices of specific grid points corresponding to kidney regions by a measurer in a manner that is comparable to that used in planimetry, but its accuracy and reliability are influenced by display window settings and grid size (Fig. 1B) [19]. The stereology method and the planimetry method are both time-consuming and require trained measurers, but they each have the advantage of excellent accuracy and repro-

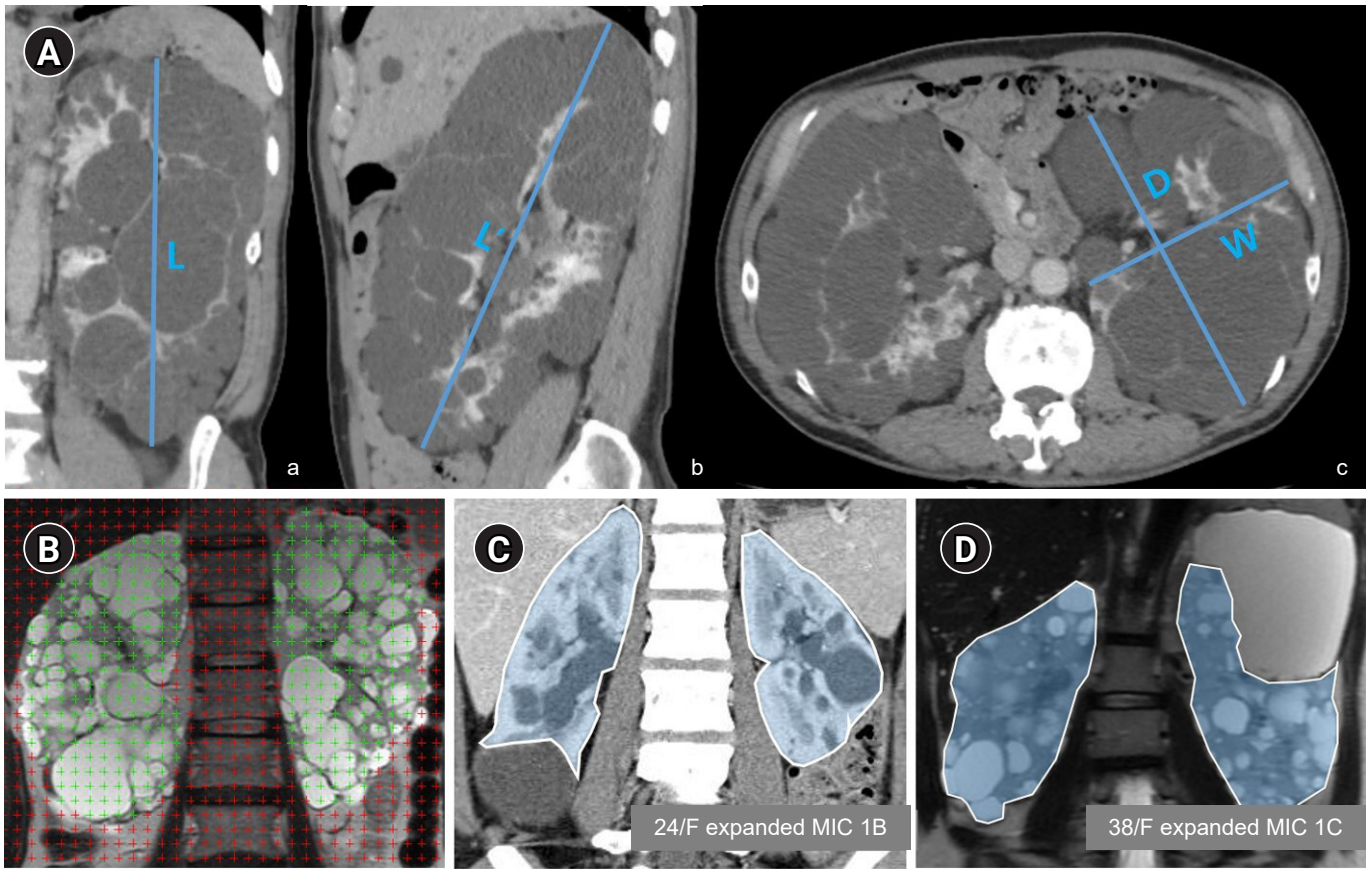

Fig. 1. Manual techniques available for estimating TKV in patients with ADPKD. (A) Ellipsoid formula applied to a coronal slice (a) and a sagittal slice (b); measurements of longitudinal length (L+L'/2), maximum width (W), and maximal depth (D) are used to calculate renal volume in the typical ADPKD calculator web-based application provided by the Mayo Polycystic Kidney Disease Center. (B) Stereology applied to a coronal slice using MRI; grid points covering both kidneys are defined. (C) Planimetry method is applied to a coronal slice on a contrast-enhanced CT image; all slices are manually traced with kidney. Coronal CT image from an expanded MIC 1B patient: a 24-year-old woman with *PKD1* gene mutation whose baseline TKV decreased from 594 mL (MIC 1C) to 389 mL (MIC 1B) after the exclusion of exophytic cysts. (D) Coronal MRI from an expanded MIC 1C patient: a 38-year-old woman with *PKD1* gene mutation whose baseline TKV decreased from 1,236 mL (MIC 1D) to 940 mL (MIC 1C) after the exclusion of exophytic cysts. TKV, total kidney volume; ADPKD, autosomal dominant polycystic kidney disease; MRI, magnetic resonance imaging; CT, computed tomography; MIC, Mayo imaging classification.

ducibility [20].

2. Evidence: markers that prove rapid progression

Evidence is a finding that appears after the onset of renal damage, so it is important to make efforts to detect it relatively early through frequent measurements.

The ERA WGIKD and the European Rare Kidney disease reference Network 2021 guidelines recommend excluding obvious slow progressors first to effectively find rapid progressors [15]. In other words, a factor is proposed to be evaluated as a candidate for treatment if the patient corresponds to the eGFR indexed by age (Table 1). If the patient in this case has sufficient renal function test results, it is possible to specifically distinguish which patient is a rapid progressor based on the annual rate of eGFR decline. In general, Kidney Disease: Improving Global Outcomes is defined as rapidly progressive CKD when the annual rate of decline in renal function is GFR ≥5 mL/min/1.73 m^2. However, in ADPKD patients, other factors— such as an increase in cyst burden—are believed to cause faster renal function deterioration. The mean annual decline in eGFR in Mayo class 1C of the MIC system was 2.53 mL/min/1.73 m^2 [11]. The average annual eGFR decline rate in the placebo group was enriched for patients with rapid progressors in the REPRISE and TEMPO 3:4 studies, where it was 3.5 mL/min/1.73 m^2 per year [3,4]. Considering these results, rapid progressors were defined as those whose ERA WGIKD in 2021 was ≥3.0 mL/min/1.73 m^2 [15]. However, the creatinine test result itself has the disadvantage of not only having day-to-day fluctuations, but also different results for each laboratory. When using the annual eGFR decline rate as evidence of rapid progression, there is a precondition that there must be five or more creatinine test results over a period of 4 years or more to compensate for the disadvantages of the creatinine test. However, patients with CKD stage 1 who do not have renal function results for a sufficient period of time in the past can be selected for treatment according to the presence or absence of MIC and other risk factors. There are also other guidelines that define a rapid progressor as one with an eGFR decline rate of >5 mL/min/1.73 m^2 for 1 year or ≥2.5 L/min/1.73 m^2 for 5 years without using eGFR indexed by age [8,14].

The TKV growth rate, or the measured rapid growth rate of TKV, can be used as evidence of rapid progression, and it refers to cases where the annual growth rate is 5% or more [21]. However, in this case, TKV should be calculated based on the results of imaging tests measured twice or more over a period of 6 months or longer [18]. The TKV value used at this time should also be the TKV value measured by planimetry or stereology.

3. Factors: markers that are suggestive-not conclusive-of rapid progression

There are certain risk factors that cannot lead to conclusive determinations of rapid progressors, but which can suggest a possibility. These risk factors help determine tolvaptan treatment when it is unclear whether the patient is a slow or rapid progressor. The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score is a score calculated using genetic findings and age in the event of high blood pressure or urology complications, and has been proposed as a prediction of the risk of rapid progression like MIC [10]. Since the effect of genotype on the rate or GFR decline is largely mediated by kidney size [13], it is reasonable to consider the PROPKD score as a factor that may increase the risk of rapid progression rather than as a risk predictor. In the absence of genetic test results, family history at least 1 first-degree relative with kidney failure before the age of 55 years can also be used as a factor influencing rapid progression [22], but extreme severity discordance is present in at least 12% of families with ADPKD [23].

How can we select patients to be treated with tolvaptan using risk, evidence, and factors?

There are seven assessment strategies—each from a different country—that use various of the clinical parameters mentioned above to select treatment patients [8,14,21,24]. One study comparing six of these strategies showed that the number of treatment patients selected according to each strategy ranged widely from 14.5% to 64.9%, thus showing a large difference [25]. As a representative example, the ERA-EDTA guideline considers changes in GFR to be particularly important, while the practical guideline in the United States considers TKV to be an important factor. The results of the selection of actual treatment patients also show differences according to the two guidelines. There are also differences between patients who actually need to receive treatment and patients who can receive treatment

according to the reimbursement agreements of their countries. There are also currently cases in which patients are not receiving appropriate treatment despite exhibiting a rapid progressor because the final treatment target has not been selected according to the insurance standard for each country, even though the patient has a treatment indication according to each guideline.

There are many practical difficulties involved in the selection of treatment patients because the parameters for the rapid progressor are very diverse, and the patient's condition can also vary substantially. There is also an urgent need to present unified international guidelines, which are currently being produced by KDIGO (https://kdigo.org/). In the present review, I will describe in three steps how to effectively select patients for treatment in an actual clinic using the risk, evidence, and factors mentioned above in an actual clinic.

1. Step 1: exclusion criteria

Before selecting a target for treatment, the first important step is to exclude patients who are not eligible for treatment. First, cases with other causes of renal function decline should be excluded from treatment (Fig. 2). In other words, individuals having which proteinuria ≥1 g/day, or having signs of accompanying vascular disease, uncontrolled severe arterial hypertension, and diabetes mellitus nephropathy that affect renal function deterioration, should be excluded from the selection of patients for treatment. Second, cases where the potential effect of delaying the dialysis period with tolvaptan treatment is judged to be

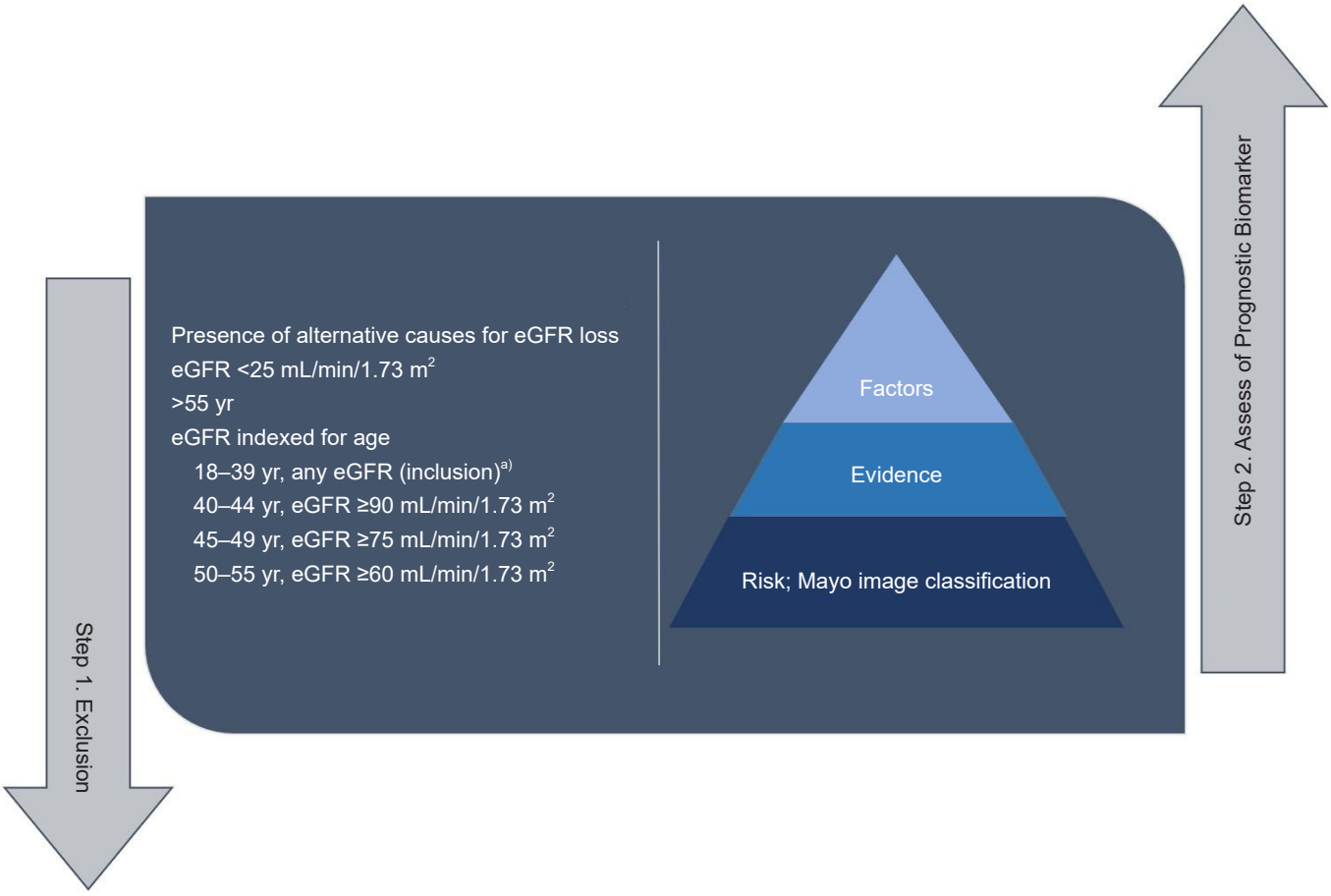

Fig. 2. STEP 1: Exclusion to treatment and assessment of prognostic biomarkers. Individuals having which proteinuria ≥1 g/day, vascular disease, uncontrolled arterial hypertension, and diabetes mellitus nephropathy that affect renal function deterioration are excluded. STEP 2: Assess the risk, evidence, and factors of rapid progression in an autosomal dominant polycystic kidney disease patient. Mayo imaging classification is the primary predictor of rapid progression. [a]Patients aged 18–39 years are not excluded regardless of the estimated glomerular filtration rate (eGFR).

very small should be excluded due to a definite slow progressor or already advanced renal damage. That is, cases with eGFR less than 25 mL/min/1.73 m^2, cases involving patients over 55 years of age with no evidence of rapid progression, and cases with an eGFR indexed for age higher than expected in individuals assessed for tolvaptan were excluded from major strategies [15,24].

2. Step 2: Assess the risk, evidence, and factors of rapid progression in an ADPKD patient

This is the process of checking the status and presence of three kinds of markers in each patient. This approach is based on the class of MIC and then finding the rapid progressors according to the presence or absence of evidence and factors (Fig. 3). In this process, a difference in treatment decisions may be observed depending on which of lower eGFR, which is useful for CKD 2-3 patients, and TKV, which can be used as an important predictor before renal function decline, are given more weight (Fig 2). In cases of MIC 1D and 1E, it is recommended to start treatment by judging it as a rapid progressor regardless of the presence or absence of evidence and factors. These cases will be the easiest to make treatment decisions. Of course, the presence of evidence and/or factors in the clinic will merit a situation in which treatment can be strongly recommended to the patient. In the ERA-EDTA 2021 guideline [15], young patients of 18 to 39 years with MIC 1D and 1E are recommended to be treated regardless of eGFR, which is considered to be a very important recommendation in terms of starting treatment to reduce cyst burden early before any structural changes appear in the kidneys. In the case of 1C, treatment is recommended if the factor exists regardless of the presence or absence of evidence. When determining the case of 1C without both evidence and factor(s), different decisions can be made depending on the strategy. In this case, follow-up of additional eGFR or TKV growth rate may be helpful. In the case of 1B with evidence, another decision can also be made according to the strategy. If eGFR is emphasized, treatment can be recommended in recognition of a rapid progressor in cases of 1B with evidence.

3. Step 3: Individualization of treatment

Because the current parameters or strategies used in rapid progressor selection are not perfect, an absolutely necessary point for patients who are not selected in the process of steps 1 and 2 is shared-decision medicine; that is, a

Risk	Evidence	Factors	Progression	Recommendation	Special consideration
1D, 1E	O	O	Rapid progressor	Indication for treatment	Treatment in >55 yr patients with evidence of rapid progression
	O	X			
	X	O			Treatment in 18–39 yr patients with any eGFR
	X	X			
1C	O	O			Treatment in >55 yr patients with evidence of rapid progression
	O	X			
	X	O	Likely rapid progressor		
	X	X	Likely slow progressor	No treatment (ERA) vs. treatment (Mayo Clinic)	Monitoring to confirm rate of progression in 2–3 yr
1B	O	O	Likely rapid progressor	Treatment (ERA) vs. no treatment (Mayo Clinic)	
	O	X			
1A, 1B	X	O	Slow progressor	No treatment	Monitoring to confirm rate of progression in 2–3 yr
	X	X			

Fig. 3. Recommendation according to the presence or absence of evidence and factors of rapid progression according to the Mayo Image Classification in selecting patients with autosomal dominant polycystic kidney disease (ADPKD) who are at risk of rapidly progressive disease for treatment with tolvaptan. Special consideration can be considered depending on the individual patient. eGFR, estimated glomerular filtration rate; ERA, European Renal Association.

process wherein the treatment process is determined together with the patient. For example, Extrapolations in the results of the REPRISE trials stated that when tolvaptan was started at an eGFR of 30 mL/min/1.73 m^2, kidney lifespan could be extended by 2.3 years [24]. This may be meaningful for some patients and may not be meaningful for other patients. It is therefore necessary for the doctor to ensure that the patient is a well-informed patient so that the patient can fully understand the pros and cons and make a decision. Patients over the age of 55 with evidence of rapid progression can also be eligible for treatment depending on the patient's physical age, degree of social activity, and motivation if there are no comorbidities [26]. Even patients who are out of the eGFR indexed for age can be considered as treatment targets if there is evidence such as eGFR decline or rapid TKV growth. Most importantly, patients with significantly higher eGFR for their age should be excluded from treatment, while patients with significantly lower eGFR compared to their age should be included in the treatment category. Even if a treatment decision has not been made at the time of evaluation, regular follow-up of eGFRs, and especially follow-up of TKV growth rates in MIC 1B/C borderline patients, are very important so that a treatment decision can be made earlier (Fig. 3) [8].

How should tolvaptan be prescribed?

There are plenty of reviews or guidelines on the actual prescription of tolvaptan [15,24,27]. In this review, we will look into the process of drug initiation and final dose selection during the actual use of tolvaptan.

1. Initiation

In the protocol of clinical studies, tolvaptan is started with the first dose of 45 mg taken early in the morning and the second of 15 mg taken 8 hours later, in the afternoon. Taking the drug twice a day suppressed 24-hour urine osmolality (Uosm), a marker of V2R inhibition, to less than 300 mOsm/kg [28]. Moreover, a higher dose early in the day and low-dose administration after 8 hours showed effective vasopressin suppression during the daytime and a gradual falling off effect during the night, thus suppressing nocturnal enuresis, which interferes with sleep [29]. Patients who are highly sensitive to tolvaptan can start at 15 mg/15 mg or 30 mg/15 mg, then gradually increase the dose to 45 mg/15 mg, 60 mg/30 mg, or 90 mg/30 mg every 1 to 4 weeks. During the first 18 months, renal function, sodium, liver function, and Uosm are checked monthly at monthly intervals, and follow-up of lipid profile and uric acid are also recommended [24,30].

2. Dose selection

It is difficult to apply a uniform dose to patients because the type and severity of aquaresis-related adverse events are different for each patient and the dose of tolvaptan that causes symptoms is different. The doses of tolvaptan that have been used in clinical studies are 120 mg in 55% to 60.6% of cases and 90 mg in 21% to 29.9% of cases [3,4]. In the first paper showing a dose dependency in the effects of tolvaptan treatment, the weight-adjusted average daily dose of tolvaptan was found to be a factor that significantly affected the change in eGFR. In a study specifically examining the subset of Japanese patients in the TEMPO 3:4 study, the increased inhibition of TKV and decreased inhibition of eGFR among Japanese patients led to the presentation of better results than the entire patient group [31]. In this study, the mean dosage of tolvaptan taken by Japanese patients was 95 mg per day, and the mean weight-adjusted dose was 1.46 mg/kg, which was higher than the 1.24 mg/kg/day reported in the entire population [32]. This suggests that a good renal outcome is good at the maximum dose, and that a weight-adjusted dose can be applied for dose selection in Asians, who are typically smaller than Westerners, who have difficulty withstanding a dose of 120 mg.

Suppressing 24-hour Uosm to less than 300 mOsm/kg means that V2R inhibition is effective, but dosing by Uosm or by changes in Uosm after starting tolvaptan is a method that has yet to be validated in clinical studies [33]. Just because Uosm is kept low does not mean that the effect of the drug should be judged as good, or that the dosage of tolvaptan should be reduced. However, the Uosm concentration can be used as a way to check whether the patient is taking the drug well, and if the Uosm concentration is high in patients maintaining a low dose, it can serve as evidence for increasing the tolvaptan dose. It is not easy to measure 24-hour Uosm in an actual clinic. If a 24-hour urine test is difficult, it is possible to see whether V2R inhibition is effective through a one-time urine Uosm measurement result after waking up, before taking morning medicine, or before taking afternoon medicine, which are times when

one's Uosm concentration is most likely to be high.

Conclusion

Tolvaptan treatment is often accompanied by side effects related to aquaresis, and it is a high-cost treatment that requires careful monitoring by medical staff due to the possibility of hepatotoxicity. Nevertheless, it is the only disease-modifying drug to date that has been found to prolong the patient's kidney lifespan. For more patients to receive proper treatment, medical doctors, the rest of the medical community, and patients must join forces. First, it is necessary to find new markers to simplify the assessment of rapid progression and treatment guidelines. There are a number of guidelines that can assist nephrologists in the selection and management of ADPKD patients on tolvaptan treatment. However, more simplified and highly accurate new markers and evidence-based medical guidelines are needed to accurately find rapid progressors. There may be no special problems encountered in the patient selection and treatment process, but cooperation with a PKD specialist may be necessary in some cases. Since ADPKD is not a common disease, cooperation with a PKD expert on the treatment decision process is recommended during genetic counseling including family planning, differentiation from other cystic diseases, atypical clinical features, or accurate measurement of TKV. Second, social support for treatment is necessary. In Korea, the Korean Society of Nephrology has been steadily promoting and educating the need for disease and treatment for the past several years. As a national health policy, the national insurance system has registered ADPKD as a rare and severely incurable disease, thereby easing the burden of medical expenses for ADPKD patients as well as allowing for 90-day prescriptions to be made available for a single visit after 18 months of starting tolvaptan, making it easier for patients to receive tolvaptan treatment. Finally, patients should learn about new treatments while being given accurate information about their conditions. If patients have a condition that requires tolvaptan treatment, they should decide on treatment after having a sufficient discussion with their doctor about the expected problems that may arise when receiving treatment.

Article information

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization: YJ. Resources: YJ. Visualization: YJ. Supervision: YKO. Writing - original draft: YJ. Writing - review & editing: YJ, YKO.

ORCID
Yeonsoon Jung, https://orcid.org/0000-0003-3657-7082
Yun Kyu Oh, https://orcid.org/0000-0001-8632-5743

References

1. Gabow PA. Autosomal dominant polycystic kidney disease. N Engl J Med 1993;329:332–42.
2. Chapman AB, Johnson A, Gabow PA, Schrier RW. The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. N Engl J Med 1990;323:1091–6.
3. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012;367:2407–18.
4. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med 2017;377:1930–42.
5. Barnawi RA, Attar RZ, Alfaer SS, Safdar OY. Is the light at the end of the tunnel nigh? A review of ADPKD focusing on the burden of disease and tolvaptan as a new treatment. Int J Nephrol Renovasc Dis 2018;11:53–67.
6. McBride L, Wilkinson C, Jesudason S. Management of Autosomal Dominant Polycystic Kidney Disease (ADPKD) during pregnancy: risks and challenges. Int J Womens Health 2020;12:409–22.
7. Liu F, Feng C, Shen H, Fu H, Mao J. Tolvaptan in pediatric autosomal dominant polycystic kidney disease: from here to where? Kidney Dis (Basel) 2021;7:343–9.
8. Chebib FT, Torres VE. Assessing risk of rapid progression in autosomal dominant polycystic kidney disease and special

considerations for disease-modifying therapy. Am J Kidney Dis 2021;78:282–92.
9. Spithoven EM, Kramer A, Meijer E, Orskov B, Wanner C, Caskey F, et al. Analysis of data from the ERA-EDTA Registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease. Kidney Int 2014;86:1244–52.
10. Cornec-Le Gall E, Audrezet MP, Rousseau A, Hourmant M, Renaudineau E, Charasse C, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2016;27:942–51.
11. Irazabal MV, Rangel LJ, Bergstralh EJ, Osborn SL, Harmon AJ, Sundsbak JL, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. J Am Soc Nephrol 2015;26:160–72.
12. Park HC, Hong Y, Yeon JH, Ryu H, Kim YC, Lee J, et al. Mayo imaging classification is a good predictor of rapid progress among Korean patients with autosomal dominant polycystic kidney disease: results from the KNOW-CKD study. Kidney Res Clin Pract 2022;41:432–41.
13. Yu AS, Shen C, Landsittel DP, Grantham JJ, Cook LT, Torres VE, et al. Long-term trajectory of kidney function in autosomal-dominant polycystic kidney disease. Kidney Int 2019;95:1253–61.
14. Soroka S, Alam A, Bevilacqua M, Girard LP, Komenda P, Loertscher R, et al. Updated Canadian expert consensus on assessing risk of disease progression and pharmacological management of autosomal dominant polycystic kidney disease. Can J Kidney Health Dis 2018;5:2054358118801589.
15. Muller RU, Messchendorp AL, Birn H, Capasso G, Cornec-Le Gall E, Devuyst O, et al. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. Nephrol Dial Transplant 2022;37:825–39.
16. Bae KT, Shi T, Tao C, Yu AS, Torres VE, Perrone RD, et al. Expanded imaging classification of autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2020;31:1640–51.
17. King BF, Reed JE, Bergstralh EJ, Sheedy PF 2nd, Torres VE. Quantification and longitudinal trends of kidney, renal cyst, and renal parenchyma volumes in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2000;11:1505–11.
18. Kistler AD, Poster D, Krauer F, Weishaupt D, Raina S, Senn O, et al. Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months. Kidney Int 2009;75:235–41.
19. Bae KT, Commean PK, Lee J. Volumetric measurement of renal cysts and parenchyma using MRI: phantoms and patients with polycystic kidney disease. J Comput Assist Tomogr 2000;24:614–9.
20. Magistroni R, Corsi C, Marti T, Torra R. A review of the imaging techniques for measuring kidney and cyst volume in establishing autosomal dominant polycystic kidney disease progression. Am J Nephrol 2018;48:67–78.
21. Horie S, Mochizuki T, Muto S, Hanaoka K, Fukushima Y, Narita I, et al. Evidence-based clinical practice guidelines for polycystic kidney disease 2014. Clin Exp Nephrol 2016;20:493–509.
22. Barua M, Cil O, Paterson AD, Wang K, He N, Dicks E, et al. Family history of renal disease severity predicts the mutated gene in ADPKD. J Am Soc Nephrol 2009;20:1833–8.
23. Lanktree MB, Guiard E, Li W, Akbari P, Haghighi A, Iliuta IA, et al. Intrafamilial variability of ADPKD. Kidney Int Rep 2019;4:995–1003.
24. Chebib FT, Perrone RD, Chapman AB, Dahl NK, Harris PC, Mrug M, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. J Am Soc Nephrol 2018;29:2458–70.
25. Wulfmeyer VC, Auber B, Haller H, Schmitt R. Comparison of different selection strategies for tolvaptan eligibility among autosomal dominant polycystic kidney disease patients. Am J Nephrol 2019;50:281–90.
26. Radhakrishnan Y, Duriseti P, Chebib FT. Management of autosomal dominant polycystic kidney disease in the era of disease-modifying treatment options. Kidney Res Clin Pract 2022;41:422–31.
27. Zhou JX, Torres VE. Autosomal dominant polycystic kidney disease therapies on the horizon. Adv Kidney Dis Health 2023;30:245–60.
28. Devuyst O, Torres VE. Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. Curr Opin Nephrol Hypertens 2013;22:459–70.
29. Shoaf SE, Chapman AB, Torres VE, Ouyang J, Czerwiec FS. Pharmacokinetics and pharmacodynamics of tolvaptan in autosomal dominant polycystic kidney disease: phase 2 trials for dose selection in the pivotal phase 3 trial. J Clin Pharmacol 2017;57:906–17.
30. Watkins PB, Lewis JH, Kaplowitz N, Alpers DH, Blais JD, Smotzer DM, et al. Clinical pattern of tolvaptan-associated liver injury in subjects with autosomal dominant polycystic kidney disease: analysis of clinical trials database. Drug Saf 2015;38:1103–13.

31. Muto S, Kawano H, Higashihara E, Narita I, Ubara Y, Matsuzaki T, et al. The effect of tolvaptan on autosomal dominant polycystic kidney disease patients: a subgroup analysis of the Japanese patient subset from TEMPO 3:4 trial. Clin Exp Nephrol 2015;19:867–77.
32. Akihisa T, Manabe S, Kataoka H, Makabe S, Yoshida R, Ushio Y, et al. Dose-dependent effect of tolvaptan on renal prognosis in patients with autosomal dominant polycystic kidney disease. Kidney360 2021;2:1148–51.
33. Devuyst O, Chapman AB, Gansevoort RT, Higashihara E, Perrone RD, Torres VE, et al. Urine osmolality, response to tolvaptan, and outcome in autosomal dominant polycystic kidney disease: results from the TEMPO 3:4 trial. J Am Soc Nephrol 2017;28:1592–602.