Use of tolvaptan in autosomal polycystic kidney disease: A single center experience

Otomozal dominant polikistik böbrek hastalığında tolvaptan kullanımı: Tek merkez deneyimi

Abstract

Aim: Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disease that progresses to end-stage renal disease (ESRD). Tolvaptan is a disease-modifying agent that slows cyst growth and kidney disease progression in ADPKD. In this study, we examined the effects and side effects of tolvaptan in high-risk ADPKD patients using tolvaptan. We share our experience of this study.

Methods: Twenty-seven ADPKD patients who were at high risk according to the Mayo Clinical Classification and accepted treatment were included in the study. Tolvaptan 60 mg/day orally was started in patients to slow the ADPKD. The daily dose was increased to 120 mg depending on the patients' response to tolvaptan treatment and their tolerance to side effects. The patients were followed up during tolvaptan treatment to observe the effects and side effects of the medication.

Results: The mean age of the patients was 40.3±8.2. Hypertension was present in 81.5% of the patients, and they mostly used renin angiotensin aldosterone system inhibitors. As aquaretic side effects of tolvaptan treatment, there was thirst in 14 patients (51.9%), polydipsia in 10 patients (37%), dry mouth in 5 patients (18.5%), and nocturia in 4 patients (14.8%). In addition, although liver enzyme elevation, hypernatremia, and acute kidney injury were observed in one patient each, these side effects did not lead to permanent discontinuation of the drug. Polyuria was observed in all patients, but the patients tolerated the polyuria well and continued to use tolvaptan treatment.

Conclusion: Although the patients experienced side effects related to tolvaptan treatment, none of the patients discontinued the drug permanently. We observed that patients generally tolerated tolvaptan treatment well.

Keywords: Autosomal dominant polycystic kidney disease; polyuria; side effects; tolvaptan

Öz

Amaç: Otozomal dominant polikistik böbrek hastalığı (ODPBH) son dönem böbrek hastalığına (SDBH) ilerleyen, sık görülen bir genetik hastalıktır. Tolvaptan ODPBH'de kist büyümesini ve böbrek hastalığı progresyonunu yavaşlatan bir hastalık modifiye edici ajandır. Bu çalışmada tolvaptan kullanan yüksek riskli ODPBH hastalıklarda tolvaptanın etki ve yan etkilerini inceledik. Bu çalışmaya ait deneyimimizi paylaşıyoruz.

Yöntemler: Mayo Klinik Sınıflaması'na göre yüksek riskli olan ve tedaviyi kabul eden 27 ODPBH hastası çalışmaya dâhil edildi. Hastalara ODPBH'yı yavaşlatmak için tolvaptan 60 mg/gün ağız yoluyla başlandı. Hastaların tolvaptan tedavisine cevabına ve yan etkilerini tolere edebilmelerine bağlı olarak günlük doz 120 mg'ye arttırıldı. Hastalar tolvaptan tedavisi süresince ilacın etki ve yan etkilerini gözlemlemek için takip edildi.

Bulgular: Hastaların ortalama yaşı 40,3±8,2 idi. Hipertansiyon hastaların %81,5'inde vardı ve çoğunlukla renin anjiyotensin aldosteron sistemi inhibitörlerini kullanıyorlardı. Tolvaptan tedavisinin aquaretik yan etkileri olarak; 14 hastada (%51,9) susama, 10 hastada (%37) polidipsi, 5 hastada (%18,5) ağız kuruluğu, 4 hastada (%14,8) noktüri vardı. Ek olarak birer hastada karaciğer enzim yüksekliği, hipernatremi ve akut böbrek hasarı gözlenmesine rağmen bu yan etkiler kalıcı olarak ilacın kesilmesine neden olmadı. Bütün hastalarda poliüri görüldü, ancak hastalar poliüriyi iyi tolere ederek tolvaptan tedavisini kullanmaya devam etti.

Sonuç: Hastalarda tolvaptan tedavisine bağlı yan etkiler görülmesine rağmen hiçbir hasta ilacı kalıcı olarak bırakmadı. Hastaların genel olarak tolvaptan tedavisini iyi tolere ettiğini gözlemledik.

Anahtar Sözcükler: Otozomal baskın polikistik böbrek hastalığı; poliüri; tolvaptan; yan etkiler

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. It occurs in about one out of every 1,000 live births (1). ADPKD shows an autosomal dominant inheritance pattern. Mutations in one of the two dominant genes, polycystin-1 (PC-1) encoded by polycystic kidney disease gene 1 (PKD1) on chromosome 16 and polycystin-2 (PC-2) encoded by polycystic kidney disease gene 2 (PKD2) on chromosome 4, mostly cause the disease. PKD1 mutation is more common and the disease progresses faster compared to patients with the PKD2 mutation (2, 3). Despite being hereditary, ADPKD is a significant cause of end-stage renal disease. In the United States, it accounts for approximately 5% of the incidence of dialysis patients (3). According to the 2021 registry report of the Turkish Society of Nephrology (TSN), the prevalence of ADPKD among incident hemodialysis patients in Turkey is 2.7% (4).

ADPKD is a progressive disease, and the rate of progression varies among individuals. It is essential to identify high-risk patients for disease progression (5). In the pathogenesis of ADPKD, increased intracellular cyclic adenosine monophosphate (cAMP) levels have an essential role in cyst formation. Vasopressin increases the level of cAMP through the vasopressin receptor 2 (V2R). Tolvaptan is the first V2R antagonist approved for the treatment of ADPKD and has been shown in several important studies to slow the rate of increase in total kidney volume and reduce the rate of loss of kidney function in ADPKD. However, aquaretic side effects such as polyuria, thirst, polydipsia, dry mouth, and nocturia were frequently observed in patients using tolvaptan. In addition, liver enzyme elevation was detected, which, although less common, causes drug discontinuation (6-8).

Although there are several reports of tolvaptan treatment in ADPKD, more data are needed regarding the treatment's long-term benefits and risks. This study aims to investigate drug-related side effects, treatment adherence, and temporary or permanent drug discontinuation due to side effects in ADPKD patients using tolvaptan.

MATERIAL AND METHODS

Study design and participants

This retrospective study was conducted in the nephrology outpatient clinic of a tertiary care university hospital between January 2021 and December 2022. The criteria for inclusion in the study were being between 18-55 years old, having an eGFR of 25-90 ml/min/1.73 m^2, using tolvaptan for at least six months, and being able to tolerate the maximum drug dose of 120 mg/day. Patients who missed at least two visits, could not reach the maximum dose of medication, and did not have a sociocultural level to express side effects were excluded from the study. This study was approved by Clinical Research Ethics Committee of Istanbul University-Cerrahpaşa (date: 08.08.2023, protocol no: 759966) and conducted by the 1975 Declaration of Helsinki, as revised in 2013.

Data collection

Data was collected by examining patient files and from the hospital's electronic database. Demographic data (age, gender, height, family history), comorbid conditions (hypertension (HT), coronary heart disease (CHD), diabetes mellitus (DM)), the presence of liver cysts, echocardiographic examination results, and the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) were recorded from patient files.

The height-adjusted total kidney volumes (HtTKV) were obtained using abdominal magnetic resonance imaging (MRI), and the corresponding Mayo Classifications of the patients were recorded. Laboratory data, including blood urea, serum creatinine, serum sodium, and daily urine volume, were evaluated before and after the treatment.

Polyuria, thirst, polydipsia, dry mouth, nocturia, liver enzyme elevation, hypernatremia, and acute kidney injury, which are the side effects of tolvaptan treatment, were recorded in the patient files. Data on treatment interruption and treatment discontinuation related to side effects were analyzed.

Identification of high-risk patients

The Mayo Clinic Classification which categorizes patients into five prognostic classes, ranging from the lowest to the highest risk group (Class 1A, 1B, 1C, 1D,

Table 1. Baseline demographic and clinical data of the patients

Variables	Patients (n:27)
Age, years	40.3±8.2
Male, %	55.6
Disease duration, years	14.2±7.3
Comorbid disease, %	
Hypertension	81.5
Coronary heart disease	7.4
Diabetes mellitus	3.7
Family history, %	85.2
Liver cyst, %	74.1
ACEi, ARB use, %	88.9
Mayo Classification, %	
Class 1C	29.6
Class 1D	51.9
Class 1E	18.5

ACEi: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers, n: Number, %: Percent

Table 2. Baseline and after tolvaptan treatment laboratory data of the patients.

Variables	Baseline	After treatment	p-value
Urea, mg/dL	41.0±15.6	39.9±21.2	0.572
Serum creatinine, mg/dL	1.35±0.6	1.40±0.6	0.056
eGFR, mL/min/1.73 m^2	72.3±32.8	69.1±32.8	0.055
Serum sodium, mEq/L	140.4±2.3	140.96±2.7	0.248
Urine volume, mL/day	2730.9±906.4	6079.5±1774.5	**<0.001***

eGFR: Estimated glomerular filtration rate. *: Chi-square test

Table 3. Side effects of tolvaptan treatment.

Side effects	Patient (n:27) (%)
Polyuria	27 (100)
Thirst	14 (51.9)
Polydipsia	10 (37)
Dry mouth	5 (18.5)
Nocturia	4 (14.8)
Elevated liver enzymes	1 (3.7)
Hypernatremia	1 (3.7)
Acute kidney injury	1 (3.7)

n: Number, %: Percent

1E) (5). This classification requires data on the patient's age, height, and total kidney volume (TKV). The calculation of TKV is usually performed using magnetic resonance imaging (MRI) by measuring the coronal and sagittal length, and depth, and width measurements of both kidneys (5).

In this study, measurements were obtained using MRI, and a web-based calculator was used to calculate TKVs and Mayo Classifications for each patient (5).

Procedures

The study included patients with high-risk Mayo classification classes 1C, 1D, and 1E in terms of ADPKD progression. Treatment decisions and patient follow-ups were performed by the same nephrologist. MRI scans were reported by the same radiologist. As mentioned above, a web-based calculator was used to calculate patients' TKV and Mayo classes.

It is recommended to initiate tolvaptan at a dose of 45 mg in the morning and 15 mg 8 hours later to reduce the risk of nocturia. With toleration of the medication, dose increases are recommended every four weeks, reaching a total dose of 120 mg per day (6). The patients included in our study were started on tolvaptan in accordance with these recommendations, and the dose was increased to 120 mg by titration.

Statistical Analysis

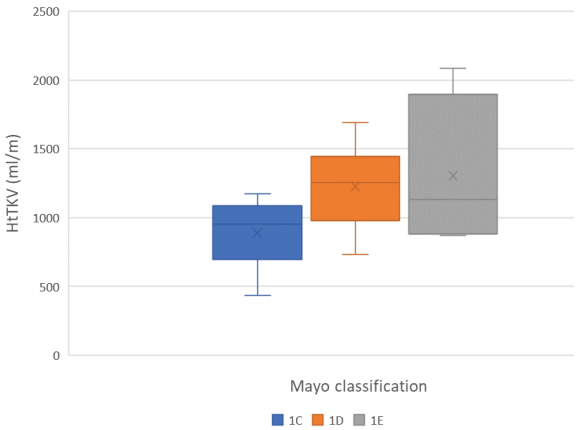
Descriptive statistics were expressed as mean standard deviation (SD) for the continuous data and as count and

proportion for the categorical data. The normality of the continuous variables was calculated using the Shapiro-Wilk test. The paired-sample t-test or Wilcoxon signed-ranks test was used to determine any significant differences between repeated measures. "Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) package program for Windows version 22.0 software (SPSS Inc., Chicago, IL, USA)" and were reported with 95% confidence intervals. Values of $p<0.05$ were considered significant.

RESULTS

A total of 27 patients (55.6% male) were included in this study. We started our study with 30 patients. However, three patients were excluded from the study because they needed to follow up after their first visit. The mean age of the patients was 40.3±8.2 years. The mean follow-up period with the diagnosis of ADPKD was 14.2±7.3 years. Hypertension was present in 81.5% of the patients, and 88.9% of them were using ACEIs/ARBs. Family history was present in 85.2% of the patients. Liver cysts accompanying renal cysts on MRI were observed in 74.1% of the patients. According to the Mayo Classification categories, the percentages of patients in Class 1C, 1D, and 1E were 29.6%, 51.9%, and 18.5%, respectively. The baseline demographic and clinical findings of the patients were given as a table (Table 1). Height-adjusted TKVs of the participants according to Mayo Classification classes were 889.6±253.3, 1227.8±280.6 and 1304±560.2 ml/m for Class 1C, 1D, and 1E, respectively (Figure 1). Echocardiographic examinations revealed left ventricular hypertrophy and mild mitral regurgitation in 7 patients (25.9%), mild tricuspid regurgitation in 2 patients (7.4%), mild aortic regurgitation and pulmonary regurgitation in 1 patient (3.7%).

In all patients, tolvaptan was initiated with a dose of 60 mg/day and gradually increased to a dose of 120 mg/day with monthly dose increments. The comparison of the laboratory data of the patient's baseline and at six months of tolvaptan treatment was given as a table (Table 2). When baseline and post-treatment values were compared, no significant difference was observed in terms of blood urea (41.0±15.6 and 39.9±21.2 mg/dL, respectively [p:0.572]), serum creatinine (1.35±0.6 and 1.40±0.6 mg/dL, respectively [p:0.056]), eGFR



HtTKV: Height-adjusted total kidney volumes

Figure 1. Boxplots showing height-adjusted total kidney volumes (HtTKV) of the participants according to Mayo Classification classes.

(72.3±32.8 and 69.1±32.8 mL/min/1.73m^2, respectively [p:0.055]), and serum sodium (140.4±2.3 and 140.96±2.7 mEq/L, respectively [p:0.248]). After tolvaptan treatment, there was a statistically significant increase in urine volume compared to baseline (2730.9±906.4 and 6079.5±1774.5 mL/day [p:<0.001]).

Side effects were given as a table (Table 3). Thirst was observed in 14 patients (51.9%), polydipsia in 10 patients (37%), dry mouth in 5 patients (18.5%), nocturia in 4 patients (14.8%), liver enzyme elevation, hypernatremia, and acute kidney injury in 1 patient (3.7%)

Treatment was interrupted temporarily in one patient with elevated liver enzymes due to a 2-fold increase in transaminase levels. This patient was restarted at a lower dose of tolvaptan and gradually increased to a dose of 120 mg/day. No recurrent transaminase increase was observed in this patient. In another patient, the daily dose was reduced from 120 mg/day to 90 mg/day due to the development of hypernatremia (serum sodium was 147 mEq/L). When the dose was increased again, no hypernatremia was observed. In 1 patient, there was an increase in serum creatinine of more than 30%, and the treatment was temporarily interrupted. The treatment was restarted, and the dose of 120 mg/day could be reached gradually. All patients experienced polyuria, but there was no intolerance that required discontinuation or dose reduction of the medication. The frequency of hematuria, flank pain, or urinary tract infection did not change with treatment.

DISCUSSION AND CONCLUSION

In this study, we shared our experience with the use of tolvaptan in daily practice in the treatment of ADPKD. In our study group, tolvaptan treatment was generally well tolerated, and no major adverse events were observed that required permanent discontinuation of treatment.

Although there is variability in disease presentation in family members affected by ADPKD, positive family history is very important in the diagnosis (2, 3). HT develops in a significant amount of patients in ADPKD, and the first treatment option is ACEi/ARB (9, 10). In addition, the most common extrarenal organ involvement is the liver (11). Our results are consistent with previous studies (2, 3, 9-11), most of the patients had another family member diagnosed with ADPKD, 81.5% of the patients were hypertensive, almost all were using ACEi/ARB, and approximately 75% had liver cysts.

The preferred method to identify high-risk patients who may benefit from tolvaptan is to use the Mayo Classification system (5). The highest risk groups (1C, 1D, 1E) should be evaluated for specific treatments (6-8). In our study, approximately half of our patients consisted of Mayo class 1D patients. Tolvaptan is currently the only disease-modifying agent used in the treatment of ADPKD in our country. Tolvaptan is a V2R antagonist that inhibits the vasopressin signal that causes an increase in intracellular cAMP, which is an important step in cyst growth (12). Although polyuria may occur as an inevitable effect of V2R inhibition, this does not prevent individuals from tolerating the treatment (13,14). In our study, polyuria developed in all patients, but this condition did not result in any patient discontinuing the tolvaptan.

The positive effects of tolvaptan on cyst growth and CKD progression in high-risk ADPKD were proven in the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3:4 and REPRISE (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD) studies (6, 8). Both of these large trials reported treatment-related hepatotoxicity and aquaretic side effects. The incidence of side effects varied, with polyuria ranging from 5.3% to 38.3%, nocturia from 4.7% to 29.1%, thirst from 4% to 55.3%, polydipsia from 1.8% to 10.4%, dry mouth from 1.9% to 16%, diarrhea from 6.9% to 13%, and increased liver enzymes from 1.8% to 10.9% (6, 8). In our study group, similar aquaretic side effects and hepatotoxicity rates were observed, except for the frequency of polyuria. Unlike the aforementioned studies, all of our patients experienced polyuria, and we did not observe any cases of diarrhea as a side effect in our study.

In the TEMPO 3:4 study, elevated liver enzymes were observed in 4.9% of patients in the tolvaptan arm and 1.2% in the placebo arm (6). Due to this condition, tolvaptan had to be discontinued in 1.8% of patients. For this reason, it is recommended that the liver enzyme levels should be followed up every two weeks in the first month, monthly for up to 18 months, and then every three months for the follow-up of the patient who is started on tolvaptan (15). In another recently published study, it was observed that the increase in alanine transaminase was higher than the increase in aspartate aminotransferase in tolvaptan-induced liver toxicity (16). In another study conducted in Japan, severe liver damage and the need for liver transplantation were revealed in a patient receiving tolvaptan treatment (17). Serious liver toxicity is the most important complication that can occur in patients treated with tolvaptan. In our study, liver enzyme elevation developed in one patient (3.7%), but permanent discontinuation of the drug was not required. No patient developed severe liver damage.

Initial tolvaptan dose and dose titration are important to prevent aquaretic side effects. Nocturia significantly affects the patient's quality of life. To prevent severe nocturia, most of the daily medication dose should be taken in the morning, and the evening dose should be taken before 4 PM (18). In our study, nocturia was well tolerated, and no patient discontinued tolvaptan for this reason. Additionally, one patient each developed hypernatremia and AKI. These findings resolved with reduction of the tolvaptan dose and temporary discontinuation of tolvaptan.

Our study has some limitations. First of all, this is a retrospective study and has a limited sample size. Second, there is no patient control group in our study. ADPKD gene analysis is not performed in our institution, and it has not been performed routinely in another center as it does not change the treatment decision. Therefore, we do not have the ADPKD gene analysis information of the patients. Finally, we could

not analyze the effect of tolvaptan on CKD progression because there was no long-term follow-up. Additionally, the fact that the study was conducted at a single center, and treatment decisions and observed side effects were managed by a single physician has positively influenced the homogeneity of the study.

In conclusion, tolvaptan treatment is generally well-tolerated, and the rate of major side effects is low. Although aquaretic side effects were found to be high in our study, this did not cause treatment cessation. It is very important for all patients to be informed in detail about tolvaptan side effects so that they can tolerate tolvaptan treatment well. The resulting tolvaptan side effects should be carefully evaluated. Aquaretic side effects, hypernatremia, and AKI can be resolved with physician-patient cooperation. The presence of other hepatotoxic agents in liver enzyme elevation should be reviewed. Liver damage is the most important part of tolvaptan treatment for both the physician and the patient. Therefore, patients should be followed with strict protocols. Patients with severe enzyme elevation should not be insisted on continuing the drug.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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