CASE REPORT

Journal of Anatolian Medical Research
JAMER 2023;8(4):70-3
DOI:10.55694/jamer.1362557

Management of Liver Function Impairment Due to the Addition of Statin in A Patient Using Tolvaptan for Polycystic Kidney Disease

Tolvaptan Kullanan Polikistik Böbrek Hastasinda Statin Eklenmesine Bağlı Karaciğer Fonksiyon Bozukluğunun Yönetimi

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ÖZET

Otozomal dominant polikistik böbrek hastalığı (ODPBH) en sık görülen kalıtsal böbrek hastalığıdır ve olguların %85'inde PKD1, %10-15'inde ise PKD2 gen mutasyonu görülmektedir. ODPBH'de renal 3',5'-siklik adenozin monofosfat seviyeleri artarak kist oluşumunda önemli rol oynar. Vazopressin üretiminin, salgılanmasının veya etkisinin sürekli baskılanması kist oluşumunu engelleyerek böbrek fonksiyonunun korunmasını sağladığı gösterilmiştir. Tolvaptan kısa etkili V2R inhibitörüdür ve vazopressinin etkisini tamamen bloke ederek kist gelişimini azaltır.

Bu vakada ODPBH'de hastalık progresyonunu yavaşlatmak amacıyla tolvaptan tedavisi kullanırken, eşzamanlı Kardiyovasküler hastalık ve dislipidemi nedeniyle statin tedavisi başlanmış ancak takiplerde hepatotoksisite gelişmesine bağlı tolvaptan tedavisinin aksatılmadan devam edilmesi için statin yerine ezetimib monoterapisi tercih edilen hasta sunulmuştur.

Anahtar Kelimeler: *Tolvaptan, polikistik böbrek hastalığı, hepatotoksisite*

ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, with PKD1 mutations observed in approximately 85% of cases and PKD2 mutations in 10-15%. In ADPKD, renal levels of 3',5'-cyclic adenosine monophosphate (cAMP) increase, playing a significant role in cyst formation. It has been demonstrated that continuous suppression of vasopressin production, secretion, or its effect prevents cyst formation and preserves kidney function. Tolvaptan acts as a short-acting V2 receptor inhibitor, completely blocking the effects of vasopressin and reducing cyst development.

In this case, a patient with ADPKD was undergoing tolvaptan therapy to slow disease progression. Simultaneously, due to the presence of concomitant cardiovascular disease and dyslipidemia, statin therapy was initiated. However, hepatotoxicity was observed during follow-up, necessitating a change from statin to ezetimibe monotherapy to ensure the continuity of tolvaptan treatment.

Keywords: *Tolvaptan, polycystic kidney, hepatotoxicity*

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent hereditary kidney disorder. It is characterized by progressive renal failure that can onset at a young or advanced age, along with renal and extrarenal manifestations such as liver and pancreatic cysts, intracranial aneurysms, and cardiac valve pathologies. Approximately 85% of cases are associated with PKD1 mutations, while PKD2 mutations are observed in 10-15% of cases. According to Ravine's criteria, the diagnosis of ADPKD is made when two or more cysts are present in one or both kidneys in individuals under 30 years of age with a positive family history. For individuals aged 30 to 59, the diagnosis requires at least two cysts in each kidney, and for those over 60, a minimum of four cysts in each kidney is necessary for diagnosis. Renal distal and collecting tubules exhibit increased levels of 3',5'-cyclic adenosine monophosphate (cAMP) due to the effects of arginine vasopressin (AVP), which plays a crucial role in ADPKD-associated cyst formation. This effect can be re-

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Cite this article as: Demiray A, Koyuncu S, Ozan R, Civan M, Koçyiğit İ. Management Of Liver Function Impairment Due to The Addition of Statin In A Patient Using Tolvaptan for Polycystic Kidney Disease Rehabilitation: A Case Report JAMER 2023;8(4):70-3.

Received: 19.09.2023
Accepted: 13.11.2023
Online Published: 05.12.2023

versed by elevating intracellular calcium levels. Continuous suppression of vasopressin production, secretion, or its effect has been shown to prevent cyst formation, prolong the lifespan of experimental animals, and preserve kidney function. Tolvaptan, acting as a short-acting V2 receptor inhibitor, completely blocks the effects of vasopressin and reduces cyst development. Cardiovascular disease (CVD) remains a significant cause of morbidity and mortality in ADPKD, with high blood cholesterol levels considered a modifiable major risk factor for CVD. Statin therapy is the preferred treatment strategy for preventing CVD. However, some patients at high risk for CVD may not tolerate statin therapy. Statin therapy, used for the treatment of dyslipidemia, is associated with an increasing incidence of liver function impairment, particularly in patients with conditions such as diabetes and metabolic syndrome. Additionally, tolvaptan therapy including other lipid-lowering treatments, can also lead to liver function impairment.

Ezetimibe is used as a second-line treatment in patients who are intolerant to statins or fail to achieve the desired low-density lipoprotein cholesterol (LDL-C) reduction despite maximum tolerated statin therapy.

In this report, we present a case of ADPKD who was initiated on tolvaptan therapy to slow disease progression while simultaneously commencing statin therapy due to concomitant cardiovascular disease and dyslipidemia. However, hepatotoxicity developed during follow-up, leading to a switch from statin to ezetimibe monotherapy to ensure the continuation of tolvaptan treatment.

CASE REPORT

A 43-year-old male patient, who had been under follow-up for hypertension and ADPKD for 10 years, underwent magnetic resonance imaging (MRI) due to an annual glomerular filtration rate (eGFR) decrease of more than 5 ml/min. On MRI imaging, the Mayo score was classified as 1D, and the PROPKD score was calculated as 9 points. To slow disease progression, tolvaptan therapy was initiated at a gradually increasing dose of 120 mg/day. In the sixth month of treatment, the patient presented to the nephrology clinic with complaints of shortness of breath, palpitations, and chest pain for a week. He described the chest pain as oppressive, lasting 5-20 minutes, and radiating to the left arm. Physical examination revealed a blood pressure of 140/90 mmHg, a pulse rate of 55 bpm, oxygen saturation of 92%, agitation, cold sweats, dry mucous membranes, and dry skin. Laboratory tests showed low-density lipoprotein cholesterol 190 mg/dl, total cholesterol 321 mg/dl, triglycerides 300 mg/dl, high-density lipoprotein cholesterol 30 mg/dl, aspartate aminotransferase 56 U/L, alanine aminotransferase 75 U/L, creatinine at 1.5 mg/dl, urea 42 mg/dl, sodium 144 meq/L, C-reactive protein 25 mg/L, leukocyte count 16.500/µL, hemoglobin 16.3 g/dl, troponin 353 ng/ml, and pro-brain natriuretic peptide (proBNP) 3602 pg/ml. All other laboratory tests were reported as normal.

An electrocardiogram revealed ventricular extrasystoles, while an echocardiogram showed an ejection fraction (EF) of 40-45%, left ventricular (LV) hypertrophy, LV wall motion abnormalities, grade 1-2 mitral regurgitation (MR), ascending aortic aneurysm, and relaxation-type diastolic dysfunction. The patient underwent percutaneous transluminal coronary angioplasty (PTCA) in the intensive care unit due to coronary artery disease. During PTCA, a plaque causing 90% stenosis was observed in the left anterior descending artery (LAD). Consequently, a stent was placed in the LAD. Following PTCA, medical treatment was initiated by the cardiology department, including aspirin, metoprolol, clopidogrel, angiotensin receptor blocker, and statin therapy (Figure 1).

Troponin and proBNP levels decreased, and improvements were observed in palpitation, chest pain, and shortness of breath. In a nephrology clinic follow-up one month later, liver function tests revealed an increase of more than threefold. Therefore, the patient's statin therapy was replaced with ezetimibe while continuing tolvaptan treatment. During the second and third-month follow-up, liver function tests showed improvement, and no changes were made to the treatment. Simultaneously conducted tests indicated a reduction of more than 25% in LDL-C levels (Table 1).

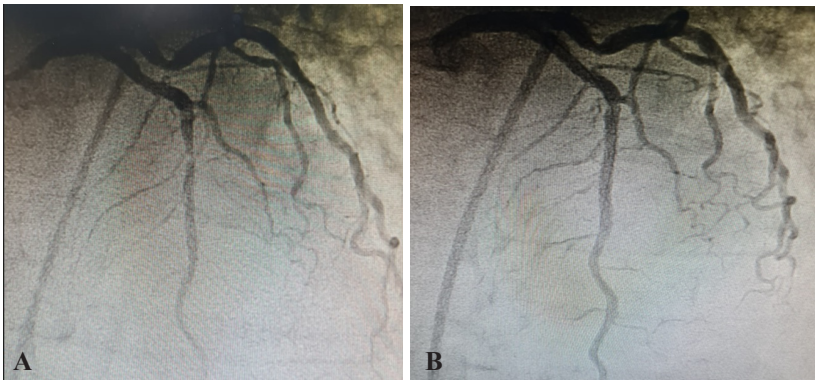

Figure 1. A- LAD occluison, **B-**Revascularization of the LAD after stent implantation

Table 1. Laboratory parameters during treatment process

Parameters	Tolvaptan Initiation	At CVD Diagnosis (Tolvaptan at 6 months)	1st Month Follow-up with Tolvaptan and Statin Treatment	2nd Month Follow-up with Tolvaptan and Ezetimibe	3rd Month Follow-up with Tolvaptan and Ezetimibe
White blood cell count (4.8-10.7x10^3/L)	6.8	16.5	5.2	8.9	6.1
Hemoglobin (14-18 gr/dl)	15.9	16.3	14.4	14.3	14.8
Platelet (130-400x10^3/L)	180	190	164	174	187
INR (0.8-1.2)	1.1	1.4	1.3	1.1	1.1
Bilurubin (0-1,4 mg/dl)	1.3	1.1	1.8	1.2	1.1
Alanine aminotransferase (0-41 ug/L)	17	75	266	54	21
Aspartate aminotransferase (0-40 ug/L)	13	56	297	77	44
Alkaline phosphatase (40-130 ug/L)	69	116	149	75	64
Creatinine (0.5-1,2 mg/dl)	1.4	1.5	1.5	1.6	1.6
Sodium (136-145 mmol/L)	137	144	141	139	140
Potassium (3.5-5.1 mmol/L)	4.5	4.8	5.1	4.6	4.1
Blood gas pH (7.35-7.45)	7.41	7.33	7.36	7.39	7.42
Troponin (0-14 ng/L)	11	353	42	15	8
Pro-BNP (0-125 pg/ml)	22	3602	1103	459	345
Low-density lipoprotein cholesterol (100-130 mg/dl)	185	190	130	135	127
Triglyceride (40-160 mg/dl)	289	300	221	237	241

CVD: *Cardiovascular disease* ***INR:*** *International Normalized Ratio*

DISCUSSION

The TEMPO study has demonstrated that tolvaptan slows down the progression to end-stage renal failure in ADPKD. In patient follow-up, liver function impairment and electrolyte disturbances have been reported as common side effects (10). In addition, in ADPKD patients, reducing LDL-C levels is targeted to reduce cardiovascular morbidity and mortality. Statins are a commonly prescribed group of medications to lower cholesterol, and treatment may need to be discontinued if side effects develop. The main reasons for discontinuing statin treatment are the presence of statin-associated muscle symptoms and the development of liver function impairment. Although the mechanisms behind these side effects are not fully understood, there is a need to identify those at high risk of developing side effects and provide alternative treatment strategies (11). Especially, the American College of Cardiology/American Heart Association guidelines recommend the use of the maximum tolerated statin dose in high-risk individuals and consider adding non-statin cholesterol-lowering drugs in situations where the risk is high. In clinical trials related to statins, asymptomatic elevations in hepatic enzyme activity, with alanine aminotransferase levels exceeding three times the upper limit of normal, can be corrected with dose reduction. When combined with elevated bilirubin, discontinuation of the statin and monitoring of liver functions are necessary. It is recommended to assess liver function tests before starting statin therapy and during the initial follow-up (12). Ezetimibe acts on the brush border of the small intestine, selectively blocking the sterol transporter Niemann-Pick C1-like 1 protein, thus selectively inhibiting both cholesterol and plant sterol absorption from the intestinal lumen into enterocytes. It has been reported to very rarely cause liver function impairment compared to statins (13). Ezetimibe can be used as a second-line treatment in patients who are intolerant to statins or do not achieve the desired LDL-C reduction despite receiving the maximum tolerated statin therapy (14).
In our case, while the patient was on tolvaptan treatment due to ADPKD, statin treatment was initiated due to high cardiovascular risk. However, due to the development of hepatotoxicity during follow-up, it was suggested to manage the clinical picture by discontinuing statin treatment and initiating ezetimibe treatment for dyslipidemia and elevated liver function tests while continuing tolvaptan treatment without interruption.

Informed Consent: Written informed consent was obtained from the subject for the publication of the study.

Conflict of Interest: The authors declare no conflict of interest in this study.

Financial Disclosure: No financial support was received from any institution or organization for this study.

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