Boosting Tolvaptan Tolerance in ADPKD: Low-Dose Hydrochlorothiazide Improves Patient Well-being Without Compromising Efficacy – A Case Report

Nefrologo in corsia

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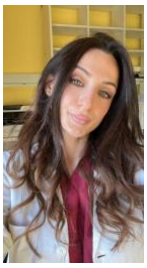
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ABSTRACT

ADPKD is the most common inherited kidney disorder, marked by numerous renal cysts, increased total kidney volume and progressive renal function decline. Mutations in the PKD1 and PKD2 genes, leading to altered cAMP signaling, drive cyst growth. Elevated antidiuretic hormone (ADH) levels further exacerbate cystogenesis. Tolvaptan, a vasopressin V2 receptor antagonist, is the only approved treatment for slowing ADPKD progression, but its use often results in significant polyuria and thirst, affecting patient quality of life.

This case report presents a 31-year-old female with ADPKD, classified as Mayo Class 1D, who showed improved tolerance to tolvaptan after co-administering low-dose hydrochlorothiazide (HCT). The patient experienced a significant reduction in polyuria and thirst while maintaining stable kidney function over four years. The annual decline in eGFR was less than expected for her disease class and improved compared to the first year of tolvaptan therapy.

This case suggests that HCT may enhance tolvaptan tolerability without reducing its efficacy. Ongoing studies, such as the HYDRO-PROTECT trial, aim to further explore the benefits of combining HCT with tolvaptan in ADPKD management.

KEYWORDS: ADPKD, tolvaptan, hydrochlorothiazide

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, accounting for about 10% of all patients worldwide who require kidney replacement therapy. ADPKD is marked by the formation of numerous cysts in the kidneys and other organs. Key characteristics include increased overall kidney volume and gradually declining kidney function [1].

ADPKD arises from mutations in the genes PKD1 or PKD2, which produce polycystin 1 (PC1) and polycystin 2 (PC2), respectively. Patients with PKD2 gene mutations typically experience a less severe form of kidney disease compared to those with PKD1 gene mutations. Additionally, evidence suggests an "allele effect" on clinical severity in individuals with PKD1 mutations. Specifically, truncating mutations are associated with more severe renal disease because they result in the complete inactivation of the gene product. The mutations' functional impact could involve altered G-protein and cAMP signaling, leading to disrupted downstream pathways and the development of cysts [2, 3].

Curiously patients with ADPKD exhibit elevated levels of ADH, which strongly correlate with the disease's severity and progression [4].

There is an urea-selective concentrating defect, which is thought to originate from the disruption of the medullary architecture by cysts, reducing the efficiency of countercurrent exchange of urea. This defect is associated with increased ADH concentrations. Therefore, ADH plays a critical role in the pathogenesis of ADPKD by promoting cyst growth and contributing to the urine-concentrating defect. Elevated ADH levels contribute to cyst growth by increasing cyclic AMP (cAMP) levels in renal tubular cells, which is the primary cause of cystogenesis [4, 5].

Tolvaptan is a medication used to treat ADPKD. It works by blocking vasopressin V2 receptors, which helps to lower cyclic AMP (cAMP) levels, slowing down the development and enlargement of cysts in the kidneys. Clinical studies have shown that tolvaptan can slow the increase in total kidney volume and the decline in kidney function, effectively delaying the progression to end-stage kidney disease (ESKD) and helping to preserve kidney function over time [6–8].

Tolvaptan is specifically indicated for adults with rapidly progressing ADPKD, identified by factors such as total kidney volume, age and renal function decline. It is taken orally in a split-dose regimen, typically twice daily, with the dose gradually increased based on the patient's tolerance and response [6].

Its effects include increased urine output (polyuria) and increased thirst, so patients always need to stay well-hydrated. Despite these effects, tolvaptan represents a significant advancement in the management of ADPKD by addressing the underlying mechanisms of cyst growth.

However, ensuring the safety and efficacy of tolvaptan requires careful patient selection and ongoing monitoring especially due to the poor tolerance related to thirst and polyuria.

Recent research has explored the potential benefits of co-prescribing hydrochlorothiazide (HCT), a thiazide diuretic commonly used to treat hypertension, to reduce polyuria and improve the tolerability of tolvaptan. HCT works by inhibiting the NaCl cotransporter in the distal convoluted tubule, reducing sodium reabsorption. This leads to extracellular volume contraction and a temporary reduction in glomerular filtration rate (GFR). As a result, increased sodium and water reabsorption occurs in the proximal tubule, less fluid reaches the collecting duct, and overall urine volume is reduced [9–11].

However, caution is warranted due to potential effects on tolvaptan efficacy. Several case reports discuss using HCT to manage tolvaptan-induced polyuria in ADPKD patients, noting also a potential

reduction in tolvaptan's effectiveness in slowing disease progression [10]. Contrary to some reported observations, as one of the leading referral centers in Italy for ADPKD, a condition that, due to its multifactorial nature, often requires a multidisciplinary approach [12], we would like to present a clinical case from our outpatient clinic where the introduction of HCT resulted in significant improvements in thirst and polyuria while maintaining tolvaptan efficacy over time.

Case report

Patient

A 31-year-old female with ADPKD, without a family history of the disease. The diagnosis was made at age 20 through ultrasound according to Ravine and Pei criteria, and confirmed by genetic testing, which identified a truncating mutation in the PKD1 gene.

Initial Treatment

At 27 years old, the patient in accordance with the ERA-EDTA criteria for the administration of tolvaptan in ADPKD began the treatment, reaching the maximum dosage of 90/30 mg within one year. At the initiation of therapy, her serum creatinine was 0.96 mg/dL, and her estimated glomerular filtration rate (eGFR calculated according to the CKD-EPI formula) was 81.1 ml/min/1.73 m². Prior to starting tolvaptan, she had experienced an annual eGFR decline greater than 2.5 ml/min/1.73m² over the previous five years, accompanied by nephromegaly. According to The Mayo Imaging Classification (MIC), which is a widely used system for categorizing disease severity based on kidney volume, adjusted for age and body surface area, she was classified as Mayo Class 1D, with an estimated TKV of about 600 mL, as assessed by magnetic resonance imaging (MRI).

Clinical Course

Following the initiation of tolvaptan, the patient reported a daily urine output of approximately 5 liters, with a consistently low urine specific gravity of 1004 and significant thirst. One year into the therapy, her serum creatinine increased to 0.99 mg/dL, and her eGFR decreased to 77.5 ml/min/1.73 m². Due to inadequate blood pressure management with an angiotensin II receptor blocker (ARB) alone, a low dosage of hydrochlorothiazide (12.5 mg per day) was incorporated into her treatment regimen. Subsequently, she achieved improved blood pressure control and experienced an immediate and significant reduction in polyuria (maximum diuresis about 3 liters a day) and thirst, while urine specific gravity, the most reliable indicator of therapeutic efficacy, remained constantly between 1002 and 1004 in serial measurements. Regrettably, for this patient, we only have access to urinary specific gravity rather than urinary osmolality, as the measurement of osmolality is not routinely performed in many regional laboratories. However, the annual decline in eGFR remained stable and below 2.5 ml/min/1.73m². As of this writing, four years since the beginning of therapy, the patient's serum creatinine is 1.04 mg/dL and eGFR is 71.5 mL/min/1.73m² (Table 1). The estimated annual decline in eGFR is approximately 2.4 mL/min/1.73m², which is less than the expected decline for this specific patient class without therapy (-3.4 mL/min/1.73m² per year) (Figure 1). It is also lower than the decline observed during the first year of therapy (3.6 mL/min/1.73m²).

Year	Creatinine (mg/dl)	eGFR (ml/min/1.73m²)	Expected eGFR (ml/min/1.73m²)
2019	0,96	81,1	81,1
2020	0,99	77,5	77,7
2021	1,01	75,5	74,3
2022	1,03	72,9	70,9
2023	1,04	71,5	67,5

Table 1. Serum creatinine, observed eGFR and expected eGFR according to Mayo Class over time

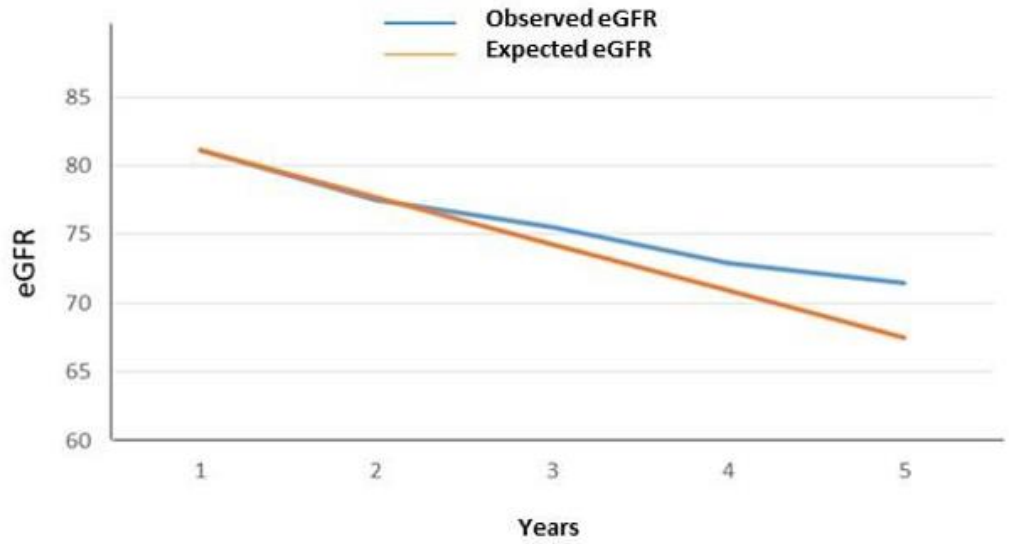

Figure 1. Observed eGFR and expected eGFR according to Mayo Class over time.

Discussion

At present, tolvaptan remains the only approved and prescribable therapy for slowing the progression of ADPKD, even in relatively advanced stages of the disease.

The TEMPO 3:4 and its extension, TEMPO 4:4, along with the REPRISE study, investigated the efficacy of tolvaptan for treating ADPKD. In TEMPO 3:4, tolvaptan was shown to slow kidney volume growth and preserve kidney function over three years, despite side effects such as thirst and polyuria. TEMPO 4:4 maintained the expected benefits on kidney function. The REPRISE study focused on patients with relatively impaired eGFR and a high likelihood of rapid disease progression, with results similar to those observed in previous trials [6].

Furthermore, the Open-Label Extension (OLE) study led by Torres provided significant insights into tolvaptan's safety and efficacy in ADPKD patients with severely reduced kidney function. This study specifically examined eGFR decline in patients with a baseline eGFR of 15 to 29 ml/min/1.73m². The findings demonstrated that starting or continuing tolvaptan therapy significantly delayed eGFR decline, even in patients with baseline eGFRs of 15 to 24 and 25 to 29 ml/min/1.73m² [13].

Therefore, the strong limitation of this therapy is closely linked to its significant aquaretic action, leading to polyuria and intense thirst, which can sometimes be incompatible with a good quality of life. There are reports suggesting that combining tolvaptan with HCT can improve these effects [9–

11]. This phenomenon might be explained by the aforementioned mechanism: HCT blocks the NaCl cotransporter in the distal convoluted tubule, leading to diminished sodium reabsorption, extracellular volume contraction which occurs along with an acute decrease in GFR. Consequently, more sodium and water are reabsorbed in the proximal tubule, less fluid is delivered to the collecting duct, and total urine volume is decreased. In this regard, also the contraction of extracellular volume initially caused by the action of tolvaptan itself can indeed explain its so-called dynamic effect, resulting at the beginning of therapy in a transient reduction of GFR.

However, it is currently unclear if the co-prescription of HCT with tolvaptan might reduce its efficacy. The limited observations available in the literature remain inconsistent. A case report in BMC Nephrology describes a 46-year-old male with ADPKD treated with tolvaptan, which caused significant polyuria. To manage hypertension, 25 mg of hydrochlorothiazide was added, reducing urine output but accelerating the decline in eGFR from −1.35 to −3.97 mL/min/1.73m² per year. The report cautions that while HCT improves tolerability by reducing polyuria, it may compromise tolvaptan's efficacy and accelerate kidney function decline. Therefore, we believe it is important to present our case report, which confirms that HCT leads to a significant improvement in thirst and polyuria without compromising the expected efficacy of tolvaptan over a relatively prolonged period and at a lower dose (12.5 mg per day vs 25 mg per day).

In our patient, classified as Mayo Class 1D, the decline in kidney function was less than expected for that specific class in the absence of therapy (-3.4 ml/min/1.73m² per year) and was also lower than the patient's annual decline before initiating tolvaptan therapy and during the first year of treatment. Notably, the estimated annual decline in eGFR was about 2.4 ml/min/1.73m², which is an improvement compared to the 4 ml/min/1.73m² decline observed in the first year of therapy, the latter likely due to the aforementioned hemodynamic effects of tolvaptan.

In essence, the slope of GFR for our patient deviates from what expected for her Mayo Class and this has not been worsened by the co-administration of HCT, demonstrating that it does not diminish its effectiveness.

We suspect that the reported reduction in tolvaptan effectiveness when co-administered with HCT in some cases may be due to HCT's potential to diminish patients' thirst sensation. This could lead individuals who typically regulate their fluid intake based on thirst to consume less fluid, potentially impacting kidney function. Therefore, we do not attribute this phenomenon to any direct interaction between HCT and tolvaptan efficacy.

Furthermore, our observations indicate a positive effect of HCT even at a very low dose (12.5 mg). It's noteworthy that in our case report, the dosage of HCT was lower compared to ongoing studies such as the important study HYDRO-PROTECT, a large-scale trial evaluating the effect of HCT co-treatment with tolvaptan in ADPKD patients. This randomized, double-blind, placebo-controlled clinical trial involves 300 ADPKD patients already on stable tolvaptan treatment, randomized to receive either 25 mg of HCT or placebo once daily for 156 weeks. The primary outcome is the rate of kidney function decline, measured by eGFR slope, with secondary outcomes including changes in quality of life and 24-hour urine volume [14].

Certainly, more controlled and randomized trials, such as the aforementioned study, are essential to further validate this effect. If confirmed, these findings could significantly improve the tolerability of therapy, boost patient adherence, and ultimately lead to better treatment outcomes. By alleviating the challenges of massive aquaresis and unrelenting thirst, this approach has the potential to enhance an already diminished quality of life and ease the psychological burden of living with such a demanding and complex disease [15].

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