CEN Case Rep (2016) 5:87–90
DOI 10.1007/s13730-015-0198-6

CASE REPORT

# Two autosomal dominant polycystic kidney (ADPKD) cases with advanced renal dysfunction, effectively treated with tolvaptan

**Hirayasu Kai[1] · Yuki Shinozaki[1] · Airi Nishikubo[1] · Megumi Watanabe[1] · Takashi Tawara[1] · Mamiko Iwase[1] · Ryouya Tsunoda[1] · Noriaki Moriyama[1] · Toshiaki Usui[1] · Tetsuya Kawamura[1] · Kei Nagai[1] · Masahiro Hagiwara[1] · Chie Saito[1] · Naoki Morito[1] · Joichi Usui[1] · Kunihiro Yamagata[1]**

Received: 28 August 2015 / Accepted: 14 September 2015 / Published online: 17 November 2015


**Abstract** We report here two cases of autosomal dominant polycystic kidney disease (ADPKD) with renal dysfunction that were treated with tolvaptan. Case 1 was a 47-year-old man with a glomerular filtration rate (GFR) of 17.0 ml/min/1.73 $m^2$ who received tolvaptan treatment (30 mg/day). After treatment, kidney pain was alleviated, and the estimated GFR (eGFR) decline improved from −9.84 ml/min/1.73 $m^2$ per year to −4.08 ml/min/1.73 $m^2$ per year, respectively. The rate of increase in total kidney volume was reduced from 18 % per year before treatment to 4 % per year following tolvaptan administration. Case 2 was a 44-year-old man with a GFR of 22.6 ml/min/1.73 $m^2$, and the eGFR decline improved from −5.76 ml/min/1.73 $m^2$ per year before treatment to −3.12 ml/min/1.73 $m^2$ per year following tolvaptan treatment (30 mg/day). The rate of increase in total kidney volume was also decreased from 10 % per year before treatment to −7 % per year following tolvaptan administration. These results suggested that tolvaptan may be effective in impeding kidney function aggravation and kidney volume increase in ADPKD patients with advanced renal dysfunction.

✉ Hirayasu Kai
hirayasu-kai06@md.tsukuba.sc.jp

[1] Division of Clinical Medicine, Department of Nephrology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan

**Keywords** Autosomal dominant polycystic kidney disease (ADPKD) · Tolvaptan · Advanced renal dysfunction

## Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is known to be caused by mutations in the PKD1 or PKD2 gene, which encodes polycystin-1 and polycystin-2 proteins, respectively. ADPKD is characterized by the progressive development of kidney and liver cysts, hypertension, and ultimately end-stage kidney disease (ESKD) [1, 2]. It is already known that tolvaptan can prevent vasopressin-mediated water reabsorption in the kidneys by competitively blocking the binding of vasopressin to its V2 receptors (V2Rs), resulting in aquaresis without changing electrolyte excretion [3, 4]. The disease changes the kidney structure and function through massive growth of numerous fluid-filled cysts and cell proliferation [1, 5]. Higher rates of kidney enlargement and larger kidney volume in Japanese ADPKD patients are associated with a more rapid decrease in kidney function [6]. In the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Outcome (TEMPO) 3:4 trial, treatment with tolvaptan for 36 months slowed the increase in total kidney volume (TKV) (the primary endpoint) and the decline in kidney function, and reduced associated symptoms (the composite secondary endpoint) in patients with ADPKD [7]. However, its effect in patients with severe renal dysfunction is not clear because the large-scale clinical intervention study was intended for cases with a glomerular filtration rate (GFR) of more than 60 ml/min/1.73 $m^2$. Thus, we herein performed tolvaptan treatment in ADPKD patients with advanced renal dysfunction.

## Case report

### Case 1

A 47-year-old man was diagnosed with ADPKD at the outpatient department of our hospital in 2010. He had a family history of this disease as his mother was also treated for ADPKD. He had hypertension, and was treated by dietary and drug therapies involving nifedipine (40 mg/day) and olmesartan (20 mg/day). His blood pressure was 130/80 mmHg. Complication with multiple liver cysts occurred, however, no other complications including brain aneurysm and heart valve disease were present. He suffered from kidney pain around 2–3 times a month. Computed tomography (CT) examination showed enlargement of the bilateral kidneys with multiple cysts of variable sizes including bleeding cysts, and total kidney volume was 3454 ml. Table 1 shows the blood and urinalysis results before tolvaptan treatment.

The rate of increase in total kidney volume was approximately 18 % per year. Renal function was accurately evaluated using inulin clearance, and the GFR was 17.0 ml/min/1.73 $m^2$, thus, he was diagnosed with advanced renal dysfunction. Proteinuria was negative, and the stage of chronic kidney disease (CKD) of this patient was categorized as G4A1. The patient explicitly expressed his wish to undergo tolvaptan treatment for ADPKD, and after obtaining informed consent, tolvaptan was administered at 30 mg/day after confirmation of the absence of serum sodium abnormality and chronic hepatitis. About 1 month after initiation of tolvaptan treatment, the kidney pain drastically diminished. From approximately 1 year before to the initiation of therapy, the eGFR was dramatically decreasing at a rate of −9.84 ml/min/1.73 $m^2$ per year (Fig. 1). After starting the therapy, the eGFR decline improved to −4.08 ml/min/1.73 $m^2$ per year, and there was a strong correlation between reduction in eGFR decline and improvement in outcome as assessed by regression analysis before and after the therapy ($p < 0.01$). The rate of increase in total kidney volume also decreased from 18 % per year before therapy to 4 % per year after tolvaptan administration. However, the eGFR was reduced to under 15 ml/min/1.73 $m^2$ after 7 months of therapy, thus, the tolvaptan treatment was discontinued because its use is forbidden under this condition.

**Table 1** Laboratory examination on tolvaptan treatment

| | Case 1 | Case 2 |
|---|---|---|
| WBC | 4600/$mm^3$ | 5200/$mm^3$ |
| RBC | 312 × 104/$mm^3$ | 396 × 104/$mm^3$ |
| Hb | 10.5 g/dl | 11.9 g/dl |
| Ht | 31.2 % | 35.6 % |
| Plt | 26.7 × 104/$mm^3$ | 21.8 × 104/$mm^3$ |
| TP | 6.8 g/dl | 7.2 g/dl |
| Alb | 4.4 g/dl | 4.2 g/dl |
| BUN | 51.8 mg/dl | 48.1 mg/dl |
| Cr | 3.23 mg/dl | 3.19 mg/dl |
| Na | 140 mmol/l | 136 mmol/l |
| K | 4.8 mmol/l | 4.6 mmol/l |
| Cl | 111 mmol/l | 102 mmol/l |
| T-chol | 213 mg/dl | 229 mg/dl |
| UP | (–) | (–) |
| OB | (–) | (–) |
| eGFR | 17.8 ml/min/1.73 $m^2$ | 18.4 ml/min/1.73 $m^2$ |
| GFR | 17.0 ml/min/1.73 $m^2$ | 22.6 ml/min/1.73 $m^2$ |
| RBF | 82 ml/min | 94 ml/min |
| FF | 0.21 | 0.24 |

*WBC* white blood cells, *RBC* red blood cells, *Hb* hemoglobin, *Plt* platelet, *TP* total protein, *Alb* albumin, *BUN* blood urea nitrogen, *Cr* creatinine, *Na* sodium, *K* potassium, *Cl* chloride, *T-cho* total cholesterol, *UP* urinary protein, *OB* occult blood, *eGFR* estimated glomerular filtration rate, *GFR* glomerular filtration, *RBF* renal blood flow, *FF* filtration fractionation

### Case 2

A 44-year-old man was diagnosed with ADPKD by his family doctor in 2005. He had a family history of this disease which was inherited from his father. He had hypertension, and was treated by dietary and drug therapies involving enalapril (2.5 mg/day). His blood pressure was 130/80 mmHg. Complications such as brain aneurysm and heart valve disease were absent. Table 1 shows the blood and urinalysis results before tolvaptan treatment.

CT examination showed enlargement of the bilateral kidneys and the liver with multiple cysts of variable sizes, and total kidney volume was 1840 ml. The rate of increase in total kidney volume was approximately 10 % per year. The GFR as assessed by insulin clearance was 22.6 ml/

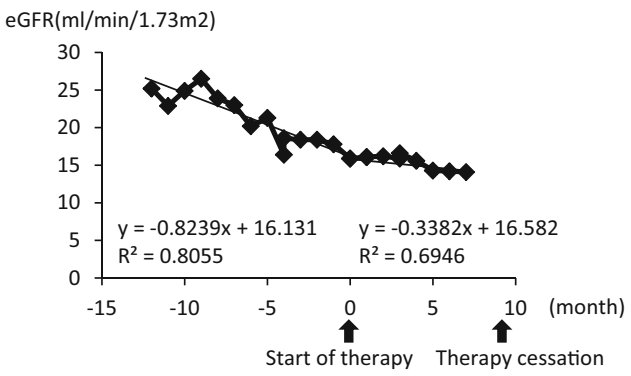


**Fig. 1** Clinical course of tolvaptan treatment eGFR in case 1

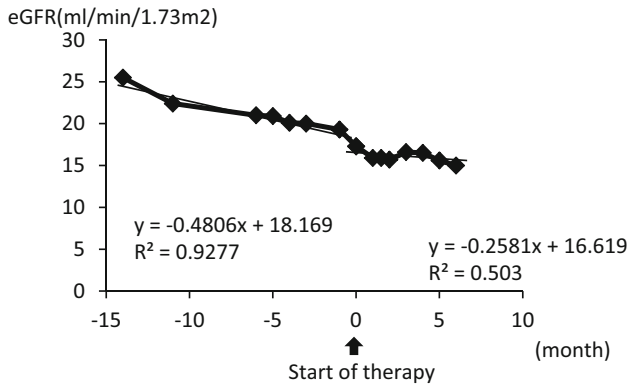


**Fig. 2** Clinical course of tolvaptan treatment eGFR in case 2

min/1.73 $m^2$, no proteinuria was observed, and the stage of CKD was categorized as G4A1. After obtaining informed consent, tolvaptan treatment was administered at 30 mg/day. The change in eGFR from approximately 1 year before and after the initiation of therapy is shown in Fig. 2. After starting the therapy, the decline in eGFR improved from −5.76 ml/min/1.73 $m^2$ per year before treatment to −3.12 ml/min/1.73 $m^2$ per year following tolvaptan administration. The rate of increase in total kidney volume was also reduced from 10 % per year to −7 % per year, respectively. Tolvaptan treatment is ongoing in this patient as his condition is stable.

## Discussion

The results of the TEMPO 3:4 trial revealed that tolvaptan is effective in alleviation of both kidney function aggravation and suppression of kidney capacity in ADPKD [7–10]. Health insurance adaptation of tolvaptan has been accepted in Japan since 2014, and it has been considered as a new therapeutic drug for ADPKD [9, 11]. However, its effect in patients with severe renal dysfunction is not clear because large-scale clinical intervention studies were intended for cases with a GFR of more than 60 ml/min/1.73 $m^2$. Thus, we investigated the effect of tolvaptan treatment on ADPKD patients with advanced renal dysfunction.

It is reported that tolvaptan treatment for ADPKD significantly controls subjective symptoms such as renal pain [7]. Renal pain is caused by the spread of cysts as well as cyst bleeding, infection and kidney stones [12]. In this study, tolvaptan treatment resulted in an improvement of renal pain in case 1. On the other hand, its effect on renal pain was not documented in case 2 because he did not feel any before the therapy. In any case, it is possible that tolvaptan contributes to improvement of renal pain in patients with advanced renal dysfunction.

Tolvaptan decreased both renal function aggravation and increase in kidney volume in these two cases, although they were not completely reverted. It was reported by the Japanese Society for Dialysis Therapy (JSDT) that the mean eGFR at introduction of dialysis in Japan is about 6 ml/min/1.73 $m^2$. In the two cases of this study, treatment with tolvaptan was estimated to postpone the start of renal replacement therapy by approximately half a year. In the future, it is necessary to reveal the effect of tolvaptan on chronic renal dysfunction.

Abnormality of the PKD1 gene is considered to contribute to a poor kidney prognosis in patients with kidney disease compared with PKD2 gene abnormality [13]. On the other hand, clinical outcome of patients with kidney disease is known to be variable even among members of the same family [14]. In other words, renal function may be different even in those of the same age and with the same kidney capacity. Renal dysfunction was similar in our two cases, but the mother of case 1 received dialysis at a young age while the father of case 2 did not receive dialysis until he was past 70 years of age. It is not clear if family history played a large role in the outcome of these two patients, thus further investigation is necessary.

Factors that are associated with poor outcome of kidney disease include high blood pressure, male gender, macroscopic hematuria [13, 15–17], and increase in kidney capacity, which were all found in our two cases. A recent study showed that rigorous blood pressure control is associated with a slower increase in total kidney volume and no overall change in the estimated GFR as compared with standard blood pressure control [18]. Cyst expansion results in a decrease in renal blood flow (RBF) [19], and in these two cases, RBF was slightly decreased in comparison to GFR and filtration fractionation (FF) was slightly increased.

Tolvaptan often causes serum sodium abnormality due to its strong diuretic effect. In addition, it is known to cause serious liver damage in around 5 % of treated patients [7]. These adverse effects did not occur in our two cases, but special attention should be paid to the occurrence of these serious adverse effects, especially in patients with advanced renal dysfunction.

In these two cases, we confirmed the efficacy of tolvaptan in two ADPKD patients with advanced renal dysfunction. Despite the low cost-effectiveness [20], it could be considered as a treatment option for advanced renal dysfunction patients who would like to prolong introduction of dialysis even by a little. To confirm its efficacy for this group of patients, it is necessary to accumulate and investigate more cases in the future.

**Acknowledgments** This case report was supported in part by a Grant-in-Aid for Research on Advanced Chronic Kidney Disease

(REACH-J), Practical Research Project for Renal Diseases from Japan Agency for Medical Research and development, AMED.

**Compliance with ethical standards**

**Conflict of interest** The authors have declared that no conflict of interest exists.

## References


1. Grantham JJ, Cook LT, Torres VE, Bost JE, Chapman AB, et al. Determinants of renal volume in autosomal-dominant polycystic kidney disease. Kidney Int. 2008;73:108–16.
2. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet. 2007;369:1287–301.
3. Yamamura Y, Nakamura S, Itoh S, Hirano T, Onogawa T, et al. OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. J Pharmacol Exp Ther. 1998;287:860–7.
4. Hirano T, Yamamura Y, Nakamura S, Onogawa T, Mori T. Effects of the V(2)-receptor antagonist OPC-41061 and the loop diuretic furosemide alone and in combination in rats. J Pharmacol Exp Ther. 2000;292:288–94.
5. Grantham JJ, Chapman AB, Torres VE. Volume progression in autosomal dominant polycystic kidney disease: the major factor determining clinical outcomes. Clin J Am Soc Nephrol. 2006;1:148–57.
6. Higashihara E, Nutahara K, Okegawa T, Shishido T, Tanbo M, et al. Kidney volume and function in autosomal dominant polycystic kidney disease. Clin Exp Nephrol. 2014;18:157–65.
7. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367:2407–18.
8. Kelsey R. Polycystic kidney disease: tolvaptan in ADPKD-TEMPO 3:4 trial results. Nat Rev Nephrol. 2013;9:1.
9. Muto S, Kawano H, Higashihara E, Narita I, Ubara Y, 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.
10. Torres VE, Gansevoort RT, Czerwiec FS. Tolvaptan in autosomal dominant polycystic kidney disease. N Engl J Med. 2013;368:1259.
11. Aihara M, Fujiki H, Mizuguchi H, Hattori K, Ohmoto K, et al. Tolvaptan delays the onset of end-stage renal disease in a polycystic kidney disease model by suppressing increases in kidney volume and renal injury. J Pharmacol Exp Ther. 2014;349:258–67.
12. Grantham JJ. Renal pain in polycystic kidney disease: when the hurt won't stop. J Am Soc Nephrol. 1992;2:1161–2.
13. Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, et al. Volume progression in polycystic kidney disease. N Engl J Med. 2006;354:2122–30.
14. Harris PC, Rossetti S. Determinants of renal disease variability in ADPKD. Adv Chronic Kidney Dis. 2010;17:131–9.
15. Gabow PA, Johnson AM, Kaehny WD, Kimberling WJ, Lezotte DC, et al. Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. Kidney Int. 1992;41:1311–9.
16. Johnson AM, Gabow PA. Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. J Am Soc Nephrol. 1997;8:1560–7.
17. Fick-Brosnahan GM, Belz MM, McFann KK, Johnson AM, Schrier RW. Relationship between renal volume growth and renal function in autosomal dominant polycystic kidney disease: a longitudinal study. Am J Kidney Dis. 2002;39:1127–34.
18. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, et al. Blood pressure in early autosomal dominant polycystic kidney disease. N Engl J Med. 2014;371:2255–66.
19. King BF, Torres VE, Brummer ME, Chapman AB, Bae KT, et al. Magnetic resonance measurements of renal blood flow as a marker of disease severity in autosomal-dominant polycystic kidney disease. Kidney Int. 2003;64:2214–21.
20. Erickson KF, Chertow GM, Goldhaber-Fiebert JD. Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. Ann Intern Med. 2013;159:382–9.