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# Tolvaptan in autosomal dominant polycystic kidney disease — a real-life experience

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## ABSTRACT

**Introduction:** Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic disease of the kidney, leading to end-stage kidney disease (ESKD) in a large proportion of affected individuals. The only approved therapy to slow the progression of chronic kidney disease (CKD) secondary to ADPKD is tolvaptan. The following analysis aimed to present the experience of the centre with tolvaptan used for ADPKD.

**Materials and methods:** Retrospective analysis of single centre data. The study group consisted of 13 patients who started treatment with tolvaptan. The control group consisted of 13 patients who refused to be treated with tolvaptan.

**Results:** In the study group, 2 patients (15%) discontinued tolvaptan due to the side effects. The intention to treat (ITT) analysis showed that among both groups progression of CKD occurred during the observation period. No statistically significant difference in the median change of estimated glomerular filtration rate (eGFR) was noticed between the study and the control group. Moreover, no statistically significant difference in the median change of eGFR was noticed between the pre-study period and the observation period both in the study group and in the control group.

**Conclusions:** According to the following results, tolvaptan is not effective in slowing the progression of CKD in patients with ADPKD in real-life settings. Further observations are needed to confirm these results.

**Keywords:** autosomal dominant polycystic kidney disease, chronic kidney disease progression, tolvaptan

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## Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic disease of the kidney, affecting approximately 1 in every 1000 people. It leads to end-stage kidney disease (ESKD) in a large proportion of affected individuals. ESKD in a course of ADPKD occurs in adulthood, and ADPKD is the fourth most common condition being a reason for the initiation of renal replacement therapy (RRT) [1, 2].

Numerous pathomechanisms of disease progression in ADPKD were described, and the elevation of cellular cyclic adenosine monophosphate mediated by arginine vasopressin is one of them [3]. Although various treatment modalities for ADPKD were proposed

[3], at the moment, the only approved therapy to slow the progression of chronic kidney disease (CKD) secondary to ADPKD is tolvaptan, an antagonist of vasopressin V2 receptor. Its effectiveness was shown in TEMPO 3:4 [4], and REPRISÉ [5] clinical trials, as well as in a long-term observational study [6]. Consequently, tolvaptan is recommended in ADPKD patients with fast progression of CKD [7]. In line with these recommendations, treatment with tolvaptan undergoes a refund in Poland, according to the decision of the Polish Ministry of Health [8].

However, the results of clinical trials are not necessarily repeatable in real-world settings [9]. This may be associated with numerous factors, e.g. influence of businesses sponsoring clinical trials, or narrow inclusion and/or exclusion criteria used in them, which limits

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the possibility of generalization of obtained results. An example is tolvaptan used for acute heart failure; according to early clinical trials, tolvaptan was beneficial in patients hospitalized for worsening heart failure in the short-term period [10]. However, at the moment, heart failure does not belong to registered indications for this medicine [11].

Therefore, the knowledge of efficacy and safety of therapies in real-world settings is of great value. This analysis aimed to present the experience of the centre with tolvaptan used for ADPKD.

## Materials and methods

It was a retrospective analysis of data of ADPKD patients treated in the outpatient department of the former Department of the Immunology, Transplantology, and Internal Diseases of the Medical University of Warsaw, Poland.

The study group consisted of patients who started treatment with tolvaptan, according to the Polish refund criteria. In short, the inclusion criteria were as follows:

- the diagnosis of ADPKD, established according to ultrasound criteria,
- 18 years old or above, and
- fast progression of CKD, defined as at least one of the following features,
  - annual decline in estimated glomerular filtration rate (eGFR)  $\geq 5$  mL/min in patients with eGFR between 30 and 90 mL/min/1.73 m<sup>2</sup>, or,
  - annual decline in eGFR  $\geq 2.5$  mL/min during the last 5 years in patients with eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup>, or,
  - annual increase in total kidney volume (TKV) assessed with magnetic resonance (MR)  $> 5\%$ , or TKV of one kidney assessed with MR  $> 750$  mL, or length of the larger kidney assessed by ultrasound  $> 16.5$  cm.

The exclusion criteria included pregnancy or breastfeeding, hypernatremia, hypotension or dehydration, eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>, liver damage, or hypersensitivity to a component of the drug.

The control group consisted of patients who fulfilled the above criteria but refused to be treated with tolvaptan due to the risk of side effects (nycturia, polyuria, need for very high fluid intake, and risk of liver damage).

All patients, both in the study and in the control group were managed by the same nephrologist (MN). The treatment was in accordance with the summary of product characteristics. Patients in the study group were informed on the dosage and timing of tolvaptan,

as well as on the need for adequate fluid intake. Patients in the study group were informed about the risk of possible drug interactions, and the need for a prompt consultation with a physician in case of appearance of symptoms of liver damage. In both groups, patients were informed on general recommendations in ADPKD, including diet, high fluid intake, healthy lifestyle, maintenance of optimal body weight, physical activity, and avoiding tobacco smoking, and alcohol overuse. In both groups, pharmacologic treatment was conducted according to patients' needs, including especially antihypertensive and lipid-lowering medicines. Patients in the study group were examined every month during the first 18 months of treatment; at each assessment, except for laboratory tests, a clinical examination was performed, including signs of dehydration.

Following data were harvested from case records: race, age, sex, height, body mass, length of the larger kidney, values of blood pressure, pharmaceuticals used, serum creatinine at the moment of initiation of tolvaptan (study group), or refusal of treatment with tolvaptan (control group), as well as at the last outpatient visit, and one visit preceding the start of observation (preferably approximately 1 year before the start of observation). Additionally, in the study group, data on serum creatinine 3 months after initiation of tolvaptan were recorded. Values of eGFR were calculated according to the CKD-EPI formula and are presented in mL/min/1.73 m<sup>2</sup>. Finally, in order to assess the rate of CKD progression, the change of eGFR per 1 patient-month in pre-study as well as during the observation period for each individual patient was calculated based on these data.

Statistical analysis was performed using Statistica 13.3 (StatSoft, Tulsa, OK, USA). The normality of data distribution was assessed with the Shapiro–Wilk test. Non-parametric tests were used in further analyses: Fisher exact test, Mann–Whitney U test, and Wilcoxon matched-pairs test, when appropriate. Results are presented as medians, range, and interquartile range (IQR). Results with  $p < 0.05$  were considered statistically significant.

The study was conducted according to the principles of the Declaration of Helsinki. The local Ethics Committee was informed about the study. Due to the character of the study, patients' written informed consent was redundant.

## Results

Thirteen patients were included in the study group and 13 in the control group. All patients were Caucasians. The characteristics of the groups are

**Table 1.** Characteristics of groups

Characteristic	Study group	Control group	p
Men/women, n(%)	7 (54%)/6 (46%)	7 (54%)/6 (46%)	NS
Median age, years (range, IQR)	43 (32–60, 14)	44 (39–63, 10)	NS
Median height, cm (range, IQR)	178 (158–192, 19)	174 (160–198, 13)	NS
Median BMI, kg/m <sup>2</sup> (range, IQR)	27.92 (21.61–32.89, 3.27)	26.73 (18.00–33.24, 3.71)	NS
Median length of the larger kidney, cm (range, IQR)	21.5 (17.5–25, 4)	20.0 (15.1–25, 5)	NS
Median eGFR, mL/min/1.73 m <sup>2</sup> (range, IQR)	31.68 (20.74–66.59, 9.76)	56.96 (21.96–74.14, 18.63)	p = 0.006
Median systolic blood pressure, mmHg (range, IQR)	130 (110–140, 8)	140 (117–150, 16)	NS
Median diastolic blood pressure, mmHg (range, IQR)	85 (60–90, 10)	90 (75–104, 11)	p = 0.042
Median time in observation, months (range, IQR)	11 (4–13, 3)	12 (3–16, 2)	NS
Median change in eGFR in the period preceding observation, mL/min/1.73 m <sup>2</sup> per 1 patient-month (range, IQR)	-0.301 (-5.430–0.519, 0.648)	-0.368 (-1.838–0.083, 0.838)	NS
<b>Pharmaceuticals</b>			
Median number of antihypertensive drugs, n (range, IQR)	3 (1–4, 1)	3 (0–4, 1)	NS
Statin use, n (%)	10 (77%)	5 (38%)	NS
Allopurinol use, n (%)	8 (62%)	2 (19%)	p = 0.021
Median number of other drugs, n (range, IQR)	1 (0–3, 3)	0 (0–2, 1)	NS

BMI — body mass index; NS— not statistically significant; IQR — interquartile range; eGFR — estimated glomerular filtration rate; CKD — chronic kidney disease

presented in Table 1. In all patients, the therapy was managed by the same physician. There were 126 and 140 patient-months of observation in the study group, and in the control group, respectively.

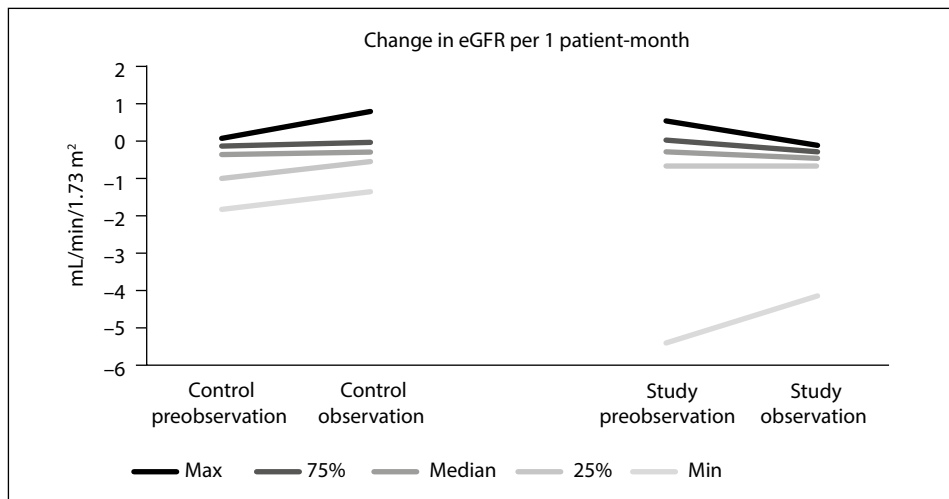
Among the study group, 2 women (15% of the group) discontinued treatment with tolvaptan due to intolerable side effects, one of them after the first day of treatment, and the second one during the second month of the therapy. Additionally, in 1 man there was an interruption in tolvaptan treatment caused by an elevation of serum aminotransferases after gastrointestinal infection, but the patient restarted treatment after normalization of aminotransferases levels.

Results of intention to treat (ITT) analysis showed that among both groups progression of CKD occurred during the observation period. In the study group, median eGFR changed from 31.68 (range 20.74–66.59, IQR 9.76) to 29.52 (19.23–49.75, 10.05) after 3 months of therapy (p = 0.02), and to 25.08 (18–49.75, 9.7) at the end of observation (p = 0.001 for the whole period of observation). Moreover, progression between month 3 and the last visit also reached statistical significance (p = 0.01). Similarly, in the control group, the progression of CKD also was statistically significant (p = 0.03), even though the median eGFR remained unchanged: median, range, and IQR of eGFR were

56.96, 21.96–74.14, and 18.63 at the beginning of the observation, and 56.96, 18.71–69.66, and 22.01 at the last visit.

Median change in eGFR per 1 patient-month during the observation period was -0.278 mL/min/1.73 m<sup>2</sup> in the control group (range from -1.378 to 0.800, IQR 0.514), and -0.444 in the study group (range from -4.210 to -0.116, IQR 0.417), including -0.680 in the study group in the first 3 months of therapy (range from -5.613 to 0.777, IQR 0.556), and -0.373 in the study group after the 3rd month of therapy (range from -4.220 to 1.855, IQR 0.661). No statistically significant difference in the median change of eGFR was noticed between the study and the control group. Moreover, no statistically significant difference in the median change of eGFR was noticed between the pre-study period and the observation period both in the study group and in the control group (Fig. 1). Additionally, no statistically significant difference was observed between the median change of eGFR during the first 3 months of therapy, and after the 3rd month of therapy in the study group.

In per protocol (PP) analysis, 11 patients with 104 patient-months of observation were included in the study group (those who continued tolvaptan at the last visit), and the control group remained unchanged, but the results were quite similar to those obtained in the ITT



**Figure 1.** Change in estimated glomerular filtration rate (eGFR) per 1 patient-month in the period preceding observation and during the observation period in the control group and in the study group

analysis. In detail, no statistically significant differences were noticed between the study group and the control group in terms of sex, age, height, body mass index (BMI), length of the larger kidney, time in observation, and change in eGFR in period preceding observation (data for the study group: sex: 7 (64%) men, and 4 (36%) women; median age 43 years (range 32–60, IQR 15); median height 182 cm (range 158–192, IQR 22); median BMI 28.06 (range 21.61–32.89, IQR 3.7); median length of the larger kidney 22 cm (range 19–25, IQR 3); median time in observation 11 months (range 4–13, IQR 8); median change in eGFR in period preceding observation  $-0.561$  mL/min/1.73 m<sup>2</sup> per 1 patient-month (range  $-5.430$ – $0.519$ , IQR 0.796). There were statistically significant differences between the study group and the control group in terms of diastolic blood pressure ( $p = 0.043$ ), statin use ( $p = 0.011$ ), and allopurinol use ( $p = 0.021$ ). In PP analysis, the median eGFR in the study group at the moment of initiation of tolvaptan was  $32.52$  mL/min/1.73 m<sup>2</sup> (range 20.74–66.59, IQR 11.73) ( $p = 0.01$  compared to the control group), and it declined to  $29.52$  mL/min/1.73 m<sup>2</sup> (range 19.23–49.75, IQR 13.49) after 3 months of therapy ( $p = 0.04$  compared to the initial value), and to  $25.08$  mL/min/1.73 m<sup>2</sup> (range 18.00–49.75, IQR 11.52) at the end of observation ( $p = 0.003$  for the whole period of observation, and  $p = 0.02$  for the comparison between month 3 and the end of observation). Finally, median change in eGFR per 1 patient-month during the observation period in the study group was  $-0.444$  mL/min/1.73 m<sup>2</sup> (range from  $-4.210$  to  $-0.198$ , IQR 0.848), including  $-0.680$  during the first 3 months of therapy (range from  $-5.613$  to  $0.777$ , IQR 2.314), and  $-0.373$  after the 3rd month of therapy

(range from  $-4.220$  to  $1.855$ , IQR 1.145). No statistically significant difference in median change in eGFR per 1 patient-month was noticed neither between the period preceding observation and observation period in the study group nor between the study group and the control group during the observation period. Moreover, no statistically significant difference in median change in eGFR per 1 patient-month was observed between the first 3 months of therapy and after the 3rd month of therapy in the study group.

## Discussion

The introduction of tolvaptan to clinical practice was a hopeful event for ADPKD patients, members of their families, and their nephrologists. However, the present results show that this optimism was previous because, in real-life settings, tolvaptan is not effective in slowing the progression of CKD in ADPKD patients. It should be noted that all patients included in this study were Caucasians, which may not reflect the situation in other populations. However, the Polish population consist of a scant per cent of other races. It should also be noted that the study group and the control group were not fully comparable, as the renal function was better in the control group. Most probably, patients with relatively preserved renal function are less prone to tolerate the adverse effects of tolvaptan. Although tolvaptan use is associated with an increased prevalence of thirst and nocturia [12], it is thought that tolvaptan does not significantly reduce patients' quality of life [13]. However, the majority of the control group could not

tolerate frequent urination during their professional activities. This was also observed in a large Canadian study [14]. Additionally, in England, more than 50% of patients abandon tolvaptan therapy within 3 years, and in 70% of them, the reason is aquaretic symptoms [15].

The difference between renal function in the study group and the control group could impact the validity of the present results. Additionally, there were statistically significant differences between the study group, and the control group in terms of diastolic blood pressure, statin use (only in PP analysis), and allopurinol use. To circumvent the problem of incomplete comparability of groups, the authors performed a comparison of the rate of progression of CKD between the pre-study period and the observation period within both the study and the control group. As no statistically significant difference in the rate of CKD progression was noted before initiation of tolvaptan and during the therapy, the efficacy of tolvaptan may be, if any, much lower than that observed in above mentioned clinical trials [4, 5], as well as in later observations [16, 17]. One possible explanation for the worsening of renal function on tolvaptan might be dehydration; however, the patients were assessed monthly, and no signs of dehydration were noticed. Additionally, it was shown that increased diuresis does not impact treatment efficacy [18]. The difference between the present results and the results of previous studies may be connected to possible additional factors determining the response to tolvaptan. Considering only genetic factors, there are over 1400 mutations leading to ADPKD [19]. In other words, ADPKD is not a homogenous disease, but as much as over 1400 subtypes of the disease may be distinguished; and, only some of them may be susceptible to the therapy with tolvaptan. If this is the case, factors determining the response to the therapy need to be identified to enable the selection of patients who will benefit from the treatment, because the administration of tolvaptan to patients who do not benefit from the therapy is connected to unjustified adverse effects and costs. As mentioned above, numerous molecular mechanisms involved in the progression of ADPKD were described [3], and different pathomechanisms may play leading roles in particular patients. If this is the case, future treatment modalities for ADPKD may include different individualized therapies for particular subgroups of ADPKD patients.

The frequency of adverse events necessitating drug discontinuation in the present group was 15%, which is in accordance with the results obtained in the TEMPO 3:4 trial, in which the rate of adverse events leading to drug discontinuation was between 14.6% in CKD Stage 2 and 17% in CKD Stage 1 [4].

The limitations of the following analysis should be acknowledged. First, the group was quite small, and

the observation period was quite short. However, the authors feel that these results are important enough to justify prompt publication. Obviously, these results should be further confirmed on larger groups, observed for longer periods. Also in the present group, the progression of CKD may slow down after a longer period on tolvaptan. According to the findings of Akihisa et al [20], who observed an initial decline in eGFR on tolvaptan and interpreted it as a reflection of the tolvaptan effect [20], a decline was expected in eGFR during the first 3 months of tolvaptan, with subsequent relative stabilization. However, the present results showed that the rate of CKD progression on tolvaptan is not differentiated between the first 3 months of therapy and the later period. Second, the present analysis was not a clinical trial; therefore, randomization was not done. Thus, the groups were not fully comparable, as discussed above. Third, the assessment of renal function might be inaccurate, as it was based on eGFR, which is a per se approximation. Moreover, inaccuracy may be differentiated between different CKD stages. Additionally, eGFR is calculated from serum creatinine, which is dependent on many factors, e.g. patient's hydration status. However, to minimize inaccuracy, all results were done in the same laboratory.

## Conclusions

The following results show that in real-world settings tolvaptan is not effective in slowing the progression of CKD in patients with ADPKD. Further observations are needed to confirm these results.

## Article information

**Data availability statement:** Data are available from the corresponding author on demand.

**Ethics statement:** The study was conducted according to the principles of the Declaration of Helsinki. The local Ethics Committee was informed about the study. Due to the character of the study, patients' written informed consent was redundant.

**Author contributions:** JB, data collection and analysis, writing the manuscript, final approval; LP, supervision, writing the manuscript, final approval; MN, idea and design of the study, patient selection, data analysis, writing the manuscript, final approval.

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**Conflict of interest:** The authors declare no conflict of interest.

**Supplementary material:** None.

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