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Principles of using tolvaptan in the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD). Recommendations of the Working Group of the Polish Society of Nephrology

Abstract

Tolvaptan, a vasopressin type 2 receptor antagonist, is currently the only disease-modifying drug available for autosomal dominant polycystic kidney disease (ADPKD). The following recommendations discuss patients' eligibility for tolvaptan treatment and its monitoring while providing a practical supplement to the Summary of Product Characteristics of the medicinal product Jinarc (Otsuka).

Key word: cysts, vaptans, aquaresis, pharmacotherapy

INTRODUCTION

Authorization of tolvaptan for the treatment of rapid progression of autosomal dominant polycystic kidney disease (ADPKD) issued by the European Medicines Agency (EMA, 2015) has changed the disease management policies in countries where reimbursement for the treatment has been provided. Thanks to the Ministry of Health's drug program (B.126), Poland has joined the list of these countries in 2021. Tolvaptan is the first disease-modifying drug available for ADPKD treatment. Previous recommendations for the management of ADPKD patients, outlined in the document of the Polish Society of Nephrology Working Group 2019 [1], were limited to nephroprotection and management of complications. Therefore, with the introduction of the B.126 program, it became necessary to develop new recommendations for the treatment of this inherited disease.

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Tolvaptan's mechanism of action involves binding to the vasopressin type 2 receptor (V2R) to block its activation (Fig. 1) [2]. V2 receptors are mainly located within the distal parts of the nephrons, where, when stimulated by vasopressin, they promote reabsorption of free water to exert an antidiuretic effect. Blocking V2R leads to aquaresis or electrolyte-sparing excretion of free water. Through the association of this receptor with adenylyl cyclase, a vasopressin-dependent increase in cyclic adenosine monophosphate (cAMP) levels is consequently blocked. cAMP controls numerous intracellular signaling pathways that promote cell proliferation, inhibition of epithelial cell apoptosis, and secretion of fluid into the renal tubules [3]. ADPKD is characterized by increased activity of these pathways. Due to the very short half-life of vasopressin, its levels cannot be measured directly, therefore, copeptin level (C-terminal fragment of preprovasopressin released along vasopressin) is used for this purpose [4]. Higher levels of plasma copeptin were observed in ADPKD patients as compared to healthy subjects [5].

Two randomized trials (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 Trial [TEMPO 3:4]) [6] and Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD [REPRISE]) [7] showed that tolvaptan inhibits the increase in kidney size and the decrease in estimated glomerular filtration rate (eGFR) in patients presenting with early (eGFR > 60 mL/min/1.73 m^2) and advanced (eGFR 25–65 mL/min/1.73 m^2) stages of the disease. Data from both studies, as well as from another long-term observational study [8], indicate a consistent and sustained effect of tolvaptan in slowing eGFR decrease by about 1 mL/min/1.73 m^2 per year as compared with the placebo group. By extrapolating the data from the aforementioned studies, we predict that starting tolvaptan treatment at an eGFR of about 60 ml/min/1.73 m^2 may delay the onset of end-stage renal failure by about seven years [9].

Tolvaptan (available in Poland under the trade name Jinarc) is indicated for the treatment of rapid progression of ADPKD. Rapid progression is defined, in Europe, as the need for renal replacement therapy before the age of 58, i.e. earlier than in the case of most ADPKD patients according to the natural history of the disease [9].

These recommendations provide a practical supplement to the Summary of Product Characteristics (SmPC) of the medicinal product Jinarc (Otsuka) [10] and are based on published data from large centers with experience in treating ADPKD as well as on the opinions of experts providing ADPKD treatment in Poland.

RECOMMENDATION 1

We recommend that the rate of disease progression be assessed in all patients diagnosed with ADPKD earlier than 55 years of age and presenting with eGFR greater than 25 mL/min/1.73 m^2 of body surface area. We recommend that the appropriateness of assessing progression in patients above the age of 55 be decided on a case-by-case basis.

The rules for diagnosing ADPKD were presented in an earlier 2019 Polish Society of Nephrology Working Group document [1].

The benefits of tolvaptan treatment in ADPKD patients with rapid disease progression, as outlined in the introduction, justify the need to provide treatment options to every patient with this diagnosis. Although patients with rapid progression represent a small subgroup of the ADPKD population, screening should be performed in all patients to select the group that could benefit from therapy as early as possible. Early initiation of tolvaptan treatment ensures cumulative benefits over time.

As shown by the results of the REPRISE trial [7], no difference in eGFR was observed between tolvaptan-treated and placebo-treated patients over the age of 55. Because in that study the group of patients at the age of > 55 years was small, it cannot be ruled out that individual patients with rapid disease progression may benefit from the treatment. The B.126 drug program does not limit access to the treatment based on age, and, therefore, in motivated patients without concomitant diseases that might affect eGFR through other mechanisms (e.g., diabetes, heart failure), evaluation of the rate of ADPKD progression may be warranted. The inclusion of the drug in this age group may offer a chance to avoid renal replacement therapy. Extending the time of conservative treatment may also, in selected cases, facilitate finding a kidney donor and anticipatory transplantation.

Table 1. Possible rapid progression of ADPKD in patients older than 39 years, based on eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [11].

Age in years	eGFR (mL/min/1.73 m²)
40–44	< 90
45–49	< 75
50–55	< 60

RECOMMENDATION 2

We recommend diagnosing rapid disease progression based on age, eGFR, and total kidney volume (TKV).

The consensus of the working group of the European Renal Association (ERA), the European Reference Network for Rare Kidney Diseases (ERKNet), and PKD International suggest that age and eGFR values are used in guiding diagnosis in ADPKD patients over 39 years of age, as presented in Table 1 [11]. In patients younger than 40, eGFR values are not useful to assess the likelihood of rapid progression. We recommend using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to estimate rapid progression.

In patients with eGFR of < 90 m/ /min/1.73 m^2, rapid progression may be evidenced by:

- An eGFR decrease of at least 5 mL/ /min/1.73 m^2 within one year in the absence of other causes (such as acute kidney injury) that can be responsible for the progression; or
- An eGFR decrease of at least 2.5 mL/ /min/1.73 m^2 per year over five years of follow-up.

The aforementioned European consensus adopts the value of ≥ 3 mL/min/1.73 m^2 per year for 4 years provided that a minimum of 5 creatinine determinations are available from this period to facilitate determination of the eGFR decline curve [11]. Rapid progression is evidenced by a linear eGFR decline greater than that expected in the course of natural disease progression (> 2.5 mL/min/1.73 m^2 per year).

The assessment of ADPKD progression as based on eGFR values has several limitations. The first is its unsuitability in patients with normal eGFR. Another is that that method provides data on past disease progression. Many patients reporting for nephrological care have no history of creatinine determinations being made over such a long period. In ADPKD patients, the diagnosis of rapid progression should not involve waiting for 4–5 years.

An imaging study with TKV evaluation should be performed in every ADPKD patient. TKV can be calculated from an MRI scan without contrast or, in patients with eGFR > 60 ml/min/1.73 m^2, from a contrast-enhanced computed tomography (CT) scan. Prognostic significance is attributed to the height adjusted TKV value (htTKV) [12]. The B.126 program makes it possible to use the ultrasound-determined greater kidney length of > 16.5 cm as an inclusion criterion.

The best predictor of future progression is the Mayo imaging classification score, with the patient's age and htTKV taken into account. A calculator for this score is available for free at http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754 [12]. To qualify the patient for the treatment, it is sufficient to use the htTKV value calculated using the ellipsoid method, in contrast to the much more time-consuming methods used to assess htTKV in research studies. Despite its unquestionable advantages, the Mayo classification is not widely available in Poland. We believe that efforts should be made to make it available at least in high-reference centers offering treatment for ADPKD patients.

In the absence of access to reliable htTKV measurements, one should assume that patients younger than 46 years of age presenting with normal renal function and htTKV of > 650 mL or renal length of > 16.5 cm as observed in ultrasound are at risk for rapid development of renal failure (experts' opinion).

RECOMMENDATION 3

In cases of ADPKD with an atypical course and when progression cannot be diagnosed using routine criteria (Recommendation 2), we recommend that additional prognostic factors (genetic testing, clinical risk factors, family history) be used.

In doubt, we suggest using other, more difficult-to-use tools to assess progression, such as the PRO-PKD (Predicting Renal Outcome in Polycystic Kidney Disease) classification [13] or the Mayo classification (Tab. 2, 3). In practice, this may mean referring the patient to a specialized center with capabilities for genetic testing or calculating TKV according to the Mayo method.

Table 2. Classification of ADPKD according to the Mayo criteria [12].

Mayo class	1A	1B	1C	1D	1E
TKV growth per year (%)	< 1.5	1.5	3 5	4.5	> 6
eGFR reduction per year (mL/min/1.73 m^2)	−0.1	−1.2	−2.5	−3.4	−4.6
Incidence of ESKD over 10 years (%)	2.4	11.0	37.8	47.1	66.9

CT — computed tomography; MRI — magnetic resonance imaging

Table 3. PRO-PKD scores for assessment of ADPKD prognosis [13].

Male: 1 point
Hypertension < 36 years of age: 2 points
First urological incident (macroscopic hematuria, back pain, cyst infection) < 35 years of age: 2 points
Pathogenic variant in PKD2 gene: 0 points
Pathogenic variant in PKD1 gene (missense)a: 2 points
Pathogenic variant in PKD1 gene (truncation)b: 4 points
A score of ≤ 3 excludes progression of PKD before the age of 60 (negative predictive value of 81.4%)
A score of > 6 is a predictor of rapid progression from ESKD before the age of 60 (positive predictive value of 90.9%)
Intermediate scores (4–6): prediction of progression uncertain

[a]Pathogenic variant resulting in an amino acid residue substitution
[b]Pathogenic variant resulting in a shorter protein product (due to a premature stop codon [nonsense mutations] or a change in the reading frame [frame--shift or splicing mutations]).

RECOMMENDATION 4

We recommend that tolvaptan treatment be offered to any patient meeting the criteria for rapid progression of ADPKD unless contraindications exist.

Any patient with rapid progression of ADPKD presenting with no contraindications for treatment as listed in the drug's SmPC should be provided with information about the benefits, risks (Tab. 4), and adverse effects of treatment with tolvaptan. The most common adverse effects include thirst, polyuria, nocturia, and pollakisuria as well as liver damage. The risk of anaphylaxis is unknown.

Tolvaptan should be given to all consenting patients with rapid disease progression who meet the criteria for inclusion in the drug program (Tab. 5).

In cases of patients with documented rapid disease progression who do not meet the criteria for inclusion in the drug program, we recommend that their physician attempt to obtain individual inclusion approval from the relevant National Health Fund branch.

RECOMMENDATION 5

We recommend aiming at the maximum daily dose (120 mg) or the maximum tolerated dose of tolvaptan.

The greatest benefit of the treatment is obtained after achieving full blockade of the V2 receptor. The majority of patients participating in the TEMPO 3:4 and REPRISE trials had received the maximum recommended dose of the drug (120 mg in two divided doses). At present, no tools are available to confirm the degree of V2R saturation with lower doses. Given the drug's pharmacokinetics, ensuring complete blockade of the V2R receptor for 24 hours is most likely possible with the highest dose of the drug.

The aquaretic effect should not be the reason for dose reduction or discontinuation of dose up-titration, as past observations indicate that the treatment tolerability improves over time. Patients should be informed of the potential benefits of maintaining the highest tolerated dose. Prescribing a reduced osmolytic load diet (limiting the quantities of sodium and simple sugars in the diet) usually alleviates the aquaretic effect. Earlier administration or reduction of the afternoon drug dose may have a beneficial effect in cases of intolerable nocturia.

Since tolvaptan is metabolized by cytochrome CYP3A, consumption of grapefruit juice is contraindicated during the treatment. Chronic use of moderate and strong CYP3A inhibitors requires a reduction in the daily tolvaptan dose.

Concomitant use of medicinal products that are moderate CYP3A inhibitors (e.g. amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) or strong CYP3A inhibi-

Table 4 Benefits and risks of ADPKD treatment with tolvaptan

Benefits	Risks
Reduced rate of kidney enlargement	Polyuria, frequent urination, nocturia
Reduced rate of eGFR decline	The need to drink plenty of fluids
Delayed requirement for renal replacement therapy	Frequent laboratory checkups (1 × per month for the first 18 months)
Reduced kidney pain	Possibility of idiosyncratic liver damage
Reduced incidence of urinary tract infections	Fatigue
Reduced risk of urolithiasis	Drug interactions (CYP3A)
	Need for contraception in women of childbearing age

Table 5. Eligibility criteria for the B. 126 drug program (overall)

1) Diagnosis of the autosomal dominant form of polycystic kidney disease (ADPKD) based on MRI or ultrasound scans (Pei-Ravine criteria)a ;
2) Age ≥ 18 years;
3) Rapid disease progression defined as:
   (a) eGFR reduction of ≥ 5 mL/min/1.73 m^2 per year and eGFR of 30–90 mL/min/1.73 m^2;
   or
   (b) eGFR reduction of ≥ 2.5 ml/min per year over 5 years and eGFR 30–60 mL/min/1.73 m^2;
   or
   (c) total kidney volume (TKV) increase of > 5% per year on MRI or TKV of one of the kidneys of > 750 mL on MRI or the length of the larger kidney of > 16.5 cm on ultrasound.

[a]Below are standardized sonographic criteria for the diagnosis and exclusion of ADPKD, along with the positive (PPV) and negative (NPV) predictive values, as well as sensitivity (SEN) and specificity (SPEC) according to the original publication by Pei et al. [16]. Unlike the classic Ravine criteria, which showed adequate sensitivity only in patients with a pathogenic variant in the PKD1 gene, the presented standardized criteria can be applied to all patients, including those without a definitive genetic diagnosis. The cited data show that the sensitivity of the sonographic criteria is age-dependent and lower in younger people, especially those under 30 years of age. The criteria are not applicable to those under the age of 15.

Confirmation of diagnosis	PKD1	PKD2	No genetic diagnosis
Age and number of cysts required to confirm diagnosis			
15–29 ≥ 3 cysts*	PPV = 100% SEN = 94.3%	PPV = 100% SEN = 69.5%	PPV = 100% SEN = 81.7%
30–39 ≥ 3 cysts*	PPV = 100% SEN = 96.6%	PPV = 100% SEN = 94.9%	PPV = 100% SEN = 95.5%
40–59 ≥ 2 cysts in each kidney	PPV = 100% SEN = 92.6%	PPV = 100% SEN = 88.8%	PPV = 100% SEN = 90%
Exclusion of diagnosis	PKD1	PKD2	No genetic diagnosis
Age and number of cysts required to confirm diagnosis			
15–29 No cysts	NPV = 99.1% SPEC = 97.6%	NPV = 83.5% SPEC = 96.6%	NPV = 90.8% SPEC = 97.1%
30–39 No cysts	NPV = 100% SPEC = 96%	NPV = 96.8% SPEC = 93.8%	NPV = 98.3% SPEC = 94.8%
40–59 No cysts	NPV = 100% SPEC = 93.9%	NPV = 100% SPEC = 93.7%	NPV = 100% SPEC = 93.9%

NPV — negative predictive value; PPV — positive predictive value; SEN — sensitivity; SPEC — specificity
*unilateral or bilateral

tors (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin) increases the risk of adverse effects and complications of tolvaptan treatment.

RECOMMENDATION 6

We recommend regular monitoring of the potential adverse effects of tolvaptan at least once a month during the first 18 months of treatment and at least once every 3 months beyond the first 18 months of treatment.

Hepatotoxicity associated with tolvaptan develops via an idiosyncratic mechanism and may occur in 5–10% of treated patients [14]. All documented cases of treatment-related increases in liver enzymes occurred within the first 18 months after treatment initiation [14]. Treatment should be discontinued if ALT or AST levels rise three-fold above the upper limit of normal [10].

In the first 3 months of treatment, a decrease in eGFR is expected and should be considered a marker of therapeutic efficacy [15].

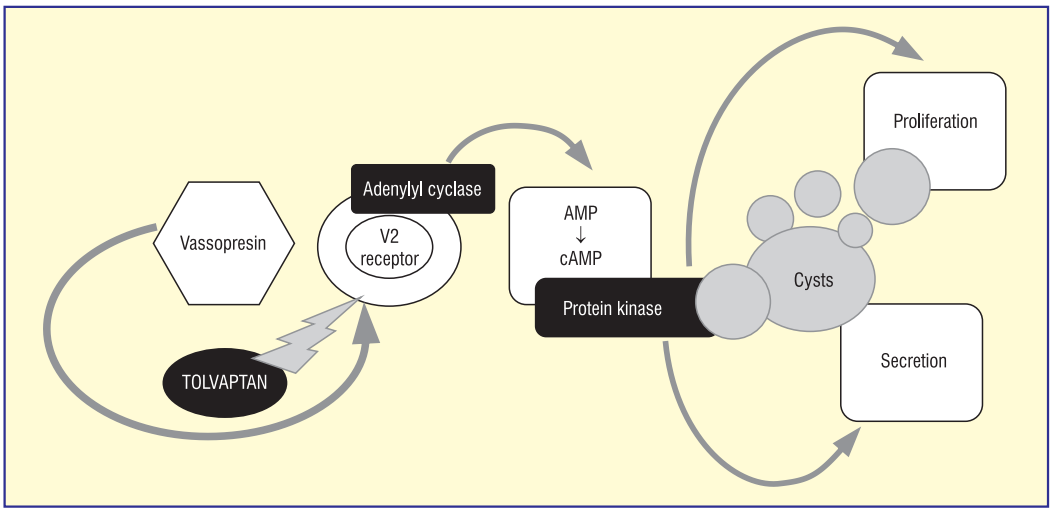

Figure 1. Simplified diagram showing the mechanism of tolvaptan's effect on ADPKD progression

A steady decline in eGFR values over the subsequent months of treatment and a decrease of more than 30% from baseline may suggest dehydration and require further diagnosis.

SUMMARY

The introduction of a V2R antagonist into the treatment regimens has changed management strategies in ADPKD patients. In every ADPKD patient, it is now necessary to rule out rapid disease progression. We recommend that the disease progression be assessed on the basis of age, eGFR, and TKV. Any patient meeting the criteria for rapid progression should be informed of the benefits and risks of tolvaptan treatment. Tolvaptan treatment should be started in all consenting patients with rapid ADPKD progression and no treatment contraindications if they meet the inclusion criteria for the B.126 drug program.

RULES

Evaluate the rate of progression in each patient.

Be mindful of the eGFR limits when qualifying for therapy.

Always evaluate TKV.

In rapid progression, include tolvaptan unless contraindications are present.

Aim at using the maximum tolerated dose of the drug.

Be mindful of possible interactions (CYP3A-mediated metabolism).

Monitor liver enzymes, hydration status, and natremia.

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