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New Options in ADPKD and How to Use them–the PROPKD Score and Beyond

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Abstract

In recent years we have not only learned about new therapy options to slow down cyst growth in ADPKD. PROPKD, a progression score which combines clinical with genetic data, has been validated, which is a tool for the nephrologist in making individual clinical decisions in favour or against (potentially harmful) long-term medications. Patient cohorts have been characterized in whom kidney size remains stable at a certain plateau for years. This article reviews the literature on these new options and discusses possible adjustments of the PROPKD score and treatment options specifically for East Asian patients. Also, a practical concept for the clinic is proposed regarding the best management of CKD patients with ADPKD, making use of the progression score and pharmacogenetic information.

Keywords: ADPKD; Vasopressin receptor blockers; m-Tor inhibitors; Statins; Cyst growth; Progression score; Pharmacogenetics

Introduction

Twenty-three years have passed since the identification of the *PKD2* gene on chromosome 4 [1] in addition to the *PKD1* gene on chromosome 16 which established the genetic correlate of at least two clinically distinct phenotypic progression patterns of autosomal-dominant polycystic kidney disease (ADPKD) in European families. Recent years have brought new insight regarding aetiology and progression as well as intervention studies with rapamycin, everolimus and tolvaptan aiming for slowing down cyst growth with long-term medication. Only for tolvaptan approval was achieved (2015 in Europe), however, its potential hepatotoxic adverse effects are cause for concern in many patients. This increase in treatment options on the one hand and concern about long-term side effects on the other hand means, that nephrologists call for better tools of genetic stratification and progress prediction of ADPKD-associated chronic kidney disease. Recently published trials provide new data in this regard, which will be discussed in this article. Moreover, alternative therapy options and a practical approach to the treatment of ADPKD patients are presented.

Post-hoc analyses of the HALT-PKD studies

Until recently only two different progression patterns had been known, with decline in glomerular filtration rates (GFR) being always linear but with different slopes associated with *PKD1* or *PKD2* mutations. The recently published [2] post-hoc analysis of the HALT-PKD studies suggest that another criterion plays a role: patient cohorts with non-linear GFR decline have been defined who may maintain intermittent stable GFR plateaus for years.

Characterization of these subgroups in genetic and clinical aspects could open new therapeutic approaches in coming years.

In this post-hoc analysis long-term follow-up data of patients were investigated who had been enrolled in one of the two “Halt Progression of Polycystic Kidney Disease” studies. 494 Patients from study A (younger patients with initially normal GFR) were included and 435 patients from study B (older, GFR already reduced at the start). Availability of progression data over at least 3 years as well as at least 7 GFR measurements per patient were inclusion criteria. In 22% of the younger study A patients and 13% of the older study B patients, periods of non-linear GFR decline were recorded, in 15.5% and 6%, respectively (studies A and B) these intermittently stable phases without GFR decline lasted for at least 4.5 years. Two thirds of these plateau patients from both studies had weak, so-called “non-truncating” mutations. Clinically, the following differences were noted: In study A, plateau patients had significantly smaller kidney volumes, higher renal arterial perfusion rates, lower albuminuria and body mass indices both at the beginning and at the end of the study period. In study B, plateau patients were older than those with linear GFR decline.

Apart from showing that it is not only the question of *PKD1 vs. PKD2* mutations, but also the difference between truncating and non-truncating mutations which carries important prognostic information for the nephrologist, this post-hoc analysis also provided clinical criteria (association of GFR plateaus for several years with lower BMI´s) despite the relatively short duration of the study.

Which ADPKD patients are at risk of an especially rapid decline of their GFR?

In summary of all genetic and clinical factors available at this point, a score was suggested and validated by the initiators of several multi-national ADPKD studies [3], which may assist in making the decision pro or contra additional therapeutic options such as Tolvaptan. This PROPKD score reflects the current literature and will likely be developed further in the years to come.

Tables 1 and **2** summarize the direct signs and predicting risk factors of rapid progression of ADPKD (modified after Muller, Haas and Sayer [4].

Parameters:

Table 1: Direct evidence of rapid progression of ADPKD.

Rate of GFR decline	≥ 5 mL/min/1.73 m^2 in 1 year
Average rate GFR decline	≥ 2.5 mL/min/1.73 m^2 over 5 years
Rate of kidney volume increase (in MRI)	≥ 5% increase of total kidney volume (TKV) per year

Table 2: Indirect predictors of rapid progression of ADPKD.

Genetics	Truncating *PKD1* mutations are associated with more rapid progression than non-truncating ones *PKD2* mutations are associated with the lowest progression rates.
Initial kidney size/ Mayo classification	>16.5 cm in ultrasound may be associated with more rapid progression, depending on the age at presentation. Height adjusted total kidney volume (htTKV) >600 mL/m is associated with rapid progression. (Mayo-classification: predicted progression based on one-timepoint measurement of htTKV and associated age).
Blood pressure	Arterial hypertension, especially before the age of 35 years, predicts a more rapid progression of ADPKD.
Urological complications	Early complications such as cyst haemorrhages, loin pain Flankenschmerz, episodes of makrohematurias or cyst infections, especially before the age of 35 years, predict a more rapid progression.
Sex	Male ADPKD patients show a more rapid progression than females.
PROPKD Score	Model which combines genetic information with clinical ones-first onset of urological complications and arterial hypertension, sex and age. A score >6 predicts end-stage kidney disease before the age of 60.

The ratio of *PKD1* mutations being truncating or non-truncating may be assumed to be relatively stable in any geographical region. This is reflected by another approach, which should be mentioned here although it is hardly applicable to clinical routine practice: in a computer model, which takes age, sex and the region into account, increase of TKV and GFR (GFR) decline over time may be simulated [5]. As illustrated in (**Figures 1 and 2**), the parameters are translated into coefficients which need to be estimated for each region. Obviously there seems to be a degree of uncertainty due to unpredictable novel mutations.

$$\Delta TKV = \exp[\lambda + \alpha.age + \beta.Ln(TKV_t) + \gamma.female + \delta.age.Ln(TKV)] - 500$$

Figure 1: TKV: Total kidney volume; ΔTKV: 1-year change in TKV; α: Age coefficient; β: TKV coefficient; γ: Female coefficient; δ: Age: LnTKV coefficient; λ: Intercept.

$$\Delta eGFR = \exp[\lambda + \beta.Ln(TKV)] - 60$$

Figure 2: eGFR: Estimated glomerular filtration rate; ΔeGFR: 1-year change in eGFR; TKV: Total kidney volume; β: Ln (TKV) coefficient; λ: Intercept.

How safe is a long-term treatment with tolvaptan? The REPRISE-study

Due to concerns articulated by the US Food and Drug Administration in connection with the approval, a study about efficacy and safety of Tolvaptan treatment in patients with advanced chronic kidney disease (CKD) stages was performed. The results of REPRISE (Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy) [6], a placebo-controlled multi-centre study, have now been published. ADPKD patients with CKD stages 2-4 (mean estimated GFR=41 ml/min per 1.73 m^2) were treated with initial doses of either 90 mg or 60 mg Tolvaptan in the morning and 30 mg in the evening over a period of one year. Progression of renal failure was slowed down in the Tolvaptan cohort to -2.3 ml/min per 1.73 m^2 (95% confidence interval [95% CI], −2.8 bis−1.9) as compared to -3.6 ml/min per 1.73 m^2 (95% CI, -4.1 to -3.1) in the placebo group. The difference between the groups was significant after one year and was estimated in average at 1.3 ml/min per 1.73 m^2; 95% CI, 0.9 to 1.7; P value <0.001. Based on these data Torres et al. [7] calculated postponement of kidney replacement therapy by 6.2 to 9 years, provided the long-term Tolvaptan therapy had been started at a residual GFR of 41 ml/min. They argue, that this is considerably longer than, for-instance, the postponement of kidney replacement therapy achievable by ACE blocker therapy in diabetic nephropathy which amounts to about 2 years. In 5.6% of the Tolvaptan group a (reversible) increase in serum alanine aminotransferase activity was noted, as compared with 1.2% in the placebo group. No case of severe liver failure was recorded.

Life style

As in all chronic diseases, life style factors which the patients can positively influence themselves are tremendously important. This includes salt restriction, high fluid intake of about 3l per day but also all measures of blood pressure optimization (reduction of body mass index, regular exercise, and meditation/relaxation techniques) as well as refraining from smoking. Especially these aspects which require the active input of the nephrologist for continuous motivation highlight his or her role as a person, while score results may in fact be calculated by computer

algorithms of artificial intelligence alone [8]. Since increased fluid intake results in suppression of vasopressin this approach is patho-physiologically quite similar to tolvaptan therapy (vasopressin receptor blockade). A recently launched prospective trial aims at exactly this similarity [9]: in a randomized multi-centre trial 180 ADPKD patients with a residual GFR ≥ 30 mL/min/1.73 m^2 will be treated with either standard therapy and uncontrolled fluid intake or standard therapy and an individualized, prescribed and controlled fluid intake strictly lowering the urine osmolality below 270 mOsmol/kg.

Other therapy options beyond tolvaptan

There are several papers with reports of successfully slowing down cyst growth in regional patient cohorts using compounds which may be associated with less severe risk of liver damage. Statins [10] need to be mentioned here, Octreotide [11] (in an Italian cohort, positive effect regarding liver cyst growth in ADPKD), or a compound from traditional Chinese medicine called Tripterygium wilfordii (Lei Gong Teng) [12] (Chinese cohort).

Another potentially useful therapeutic approach to slow down cyst growth might be the increase of intracellular calcium concentration, which may be achieved with calcimimetic agents or Saikosaponin-d. At least in an animal model this has been shown to lead to autophagy and subsequently decreased proliferation of ADPKD cells *via* the CaMKK β-AMPK-mTOR pathway [13]. Since allosteric activation of the calcium-sensing receptor (CaSR) by calcimimetics may be mimicked by gain-of-function single nucleotide polymorphisms (SNP) in the CaSR gene, the SNP rs1042636 is noteworthy in this regard, especially in East Asian patients. It causes a gain of function [14] and the allele frequencies are reversed between Whites/Blacks (arginine) on the one hand and East Asians (glycine) on the other hand. The glycine allele results in a more active receptor molecule, equivalent to about 30 mg of cinacalcet HCl o.d. As Jeong et al. [15] reported in a Korean dialysis patient cohort, rs1042636 is also associated with cinacalcet efficacy in these patients. Therefore, rs1042636 is a potential candidate to further improve the PROPKD score especially in East Asian patients.

Still at the experimental stage is another promising therapeutic approach which aims to utilize the extremely high expression of folate receptors in ADPKD cells: by coupling the mTor-inhibitor rapamycine with folate, much higher local concentrations of the drug within these cells might be achievable as compared with systemic administration of rapamycine alone [16].

For the sake of completeness, it should be mentioned, that Ganetespib [17] has been shown in ADPKD animal models to also slow down cyst growth.

Atypical genetic causes of polycystic kidney disease

Polycystic kidney disease with relatively slow progression to end-stage kidney failure may be due to rare mutations in genes other than *PKD1* or *PKD2*. This was reported by Cornec-Le Gall et al. [18] who found mutations of the *DNAJB11* gene in 23 members of wo families. The gene product is involved in the transport of membrane proteins from the endoplasmatic reticulum to the outer cell membrane. Seven patients of this cohort reached end-stage kidney failure at ages between 59 and 89 years. Finally, as anecdotal evidence from my own practice, the case of an 82 year old patient should be reported. She developed acute on chronic kidney failure in-the course of a urosepsis. Apparently, she had never seen a doctor in her entire life, but she reported that she could only sleep on her right side. In ultrasound a huge unilateral polycystic kidney was found which filled up the entire left side of her abdomen. Next generation sequencing of her leucocyte genome showed no abnormalities (un-published data) so that a somatic mutation of her left kidney anlage during embryogenesis needs to be assumed.

Summary

Statins, indicated for prophylaxis of coronary artery disease in any case of CKD, may possibly be of additional benefit in ADPKD by slowing down cyst growth. High fluid intake of about 3l per day should be aimed for in ADPKD and should decrease urine osmolality below 270 mOsmol/kg. Patients who can´t reach this threshold and whose PROPKD score is >6 should be considered for long-term tolvaptan therapy. In general, the more severe the polycystic kidney disease is the earlier tolvaptan should be administered, which has already been used successfully (off-label) in a new-born infant with severe polycystic kidney disease ADPKD [19].

While therapeutic options for ADPKD have increased in recent years so has the need of nephrologists to get new prognostic tools in-order to optimize therapy for each individual patient. The PROPKD score may help for the decision when to start tolvaptan. The *CaSR* gene SNP rs1042636 could possibly be used to improve the PROPKD score especially in East Asian patients.

References

1. San Millán JL, Viribay M, Peral B, Martínez I, Weissenbach J, et al. (1995) Refining the localization of the PKD2 locus on chromosome 4q by linkage analysis in Spanish families with autosomal dominant polycystic kidney disease type 2. Am J Hum Genet 56: 248-253.
2. Brosnahan GM, Abebe KZ, Moore CG, Rahbari-Oskoui FF, Bae KT, et al. (2018) HALT-PKD Trial Investigators. Patterns of kidney function decline in autosomal dominant polycystic kidney disease: a post hoc analysis from the HALT-PKD trials. Am J Kidney Dis 71: 666-676.
3. Cornec-Le Gall E, Blais JD, Irazabal MV, Devuyst O, Gansevoort RT, et al. (2017) Can we further enrich autosomal dominant polycystic kidney disease clinical trials for rapidly progressive patients? Application of the PROPKD score in the TEMPO trial. Nephrol Dial Transplant.
4. Müller RU, Haas CS, Sayer JA (2018) Practical approaches to the management of autosomal dominant polycystic kidney disease patients in the era of tolvaptan. Clin Kidney J 11: 62-69.
5. McEwan P, Bennett Wilton H, Ong ACM, Orskov B, Sandford R, et al. (2018) A model to predict disease progression in patients with

autosomal dominant polycystic kidney disease (ADPKD): the ADPKD Outcomes Model. BMC Nephrol 19: 37.

6. Mustafa RA, Yu ASL (2018) Burden of proof for tolvaptan in ADPKD: did REPRISE provide the answer? Clin J Am Soc Nephrol 13: 1107-1109.

7. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, et al. (2018) Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial. Nephrol Dial Transplant 32: 1262.

8. Niel O, Boussard C, Bastard P (2018) Artificial intelligence can predict GFR decline during the course of ADPKD. Am J Kidney Dis 71: 911-912.

9. Wong ATY, Mannix C, Grantham JJ, Allman-Farinelli M, Badve SV, et al. (2018) Randomised controlled trial to determine the efficacy and safety of prescribed water intake to prevent kidney failure due to autosomal dominant polycystic kidney disease (PREVENT-ADPKD). BMJ Open 8: e018794.

10. Cadnapaphornchai MA, George DM, McFann K, Wang W, Gitomer B, et al. (2014) Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 9: 889-896.

11. Caroli A, Antiga L, Cafaro M, Fasolini G, Remuzzi A, et al. (2010) Reducing polycystic liver volume in ADPKD: effects of somatostatin analogue octreotide. Clin J Am Soc Nephrol 5: 783-789.

12. Xue C, Zhou CC, Wu M, Mei CL (2016) The clinical manifestation and management of autosomal dominant polycystic kidney disease in China. Kidney Dis (Basel) 2: 111-119.

13. Shi W, Xu D, Gu J, Xue C, Yang B, et al. (2018) Saikosaponin-d inhibits proliferation by up-regulating autophagy via the CaMKKβ-AMPK-mTOR pathway in ADPKD cells. Mol Cell Biochem.

14. Vezzoli G, Terranegra A, Arcidiacono T, Biasion R, Coviello D, et al. (2007) R990G polymorphism of calcium-sensing receptor does produce a gain-of-function and predispose to primary hypercalciuria. Kidney Int 11: 1155-1162

15. Jeong S, Kim IW, Oh KH, Han N, Joo KW, et al. (2016) Pharmacogenetic analysis of cinacalcet response in secondary hyperparathyroidism patients. Drug Des Devel Ther 10: 2211-2225

16. Kipp KR, Kruger SL, Schimmel MF, Parker N, Shillingford JM, et al. (2018) Comparison of folate-conjugated rapamycin versus unconjugated rapamycin in an orthologous mouse model of polycystic kidney disease. Am J Physiol Renal Physiol.

17. Nikonova AS, Deneka AY, Kiseleva AA, Korobeynikov V, Gaponova A, et al. (2018) Ganetespib limits ciliation and cystogenesis in autosomal dominant polycystic kidney disease (ADPKD) FASEB J 32: 2735-2746.

18. Cornec-Le Gall E, Olson RJ, Besse W, Heyer CM, Gainullin VG, et al. (2018) Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. Am J Hum Genet 102: 832-844.

19. Olalekan K, Fox A, Gilbert R (2016) Tolvaptan use in severe neonatal autosomal dominant polycystic kidney disease (ADPKD): the pharmaceutical challenge. Arch Dis Child 101: e2.