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Autosomal dominant polycystic kidney disease (ADPKD) – targets of pharmacotherapy and extrarenal complications

Autosomalna dominująca wielotorbielowatość nerek (ADPKD) – cele farmakoterapii i powikłania pozanerkowe

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Keywords

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Słowa kluczowe

ADPKD, podłoże genetyczne, terapia celowana, objawy pozanerkowe

S u m m a r y

Autosomal dominant polycystic kidney disease (ADPKD) is hereditary cystic disorder with predominantly renal manifestation (large kidneys, flank pain, haematuria, hypertension and renal insufficiency). Some patients also present extrarenal symptoms, including hepatic cysts, cerebral and aortic aneurysms and colonic diverticula. The underlying genetic background of ADPKD is related to mutation of the *PKD1* and *PKD2* genes, coding specific protein products, known as polycystin 1 and 2. Renal failure develops mainly about the 6th decade of life. Apart from classic, symptomatic treatment of chronic kidney disease, several specific therapies, aimed to several pathways of disease mechanism, have been conducted in clinical trials, including use of ACE, mTOR, V2 receptor and cAMP inhibitors. None of those was universally effective in terms of complete stopping cysts growth and slowing deterioration of renal function or appeared to be not widely acceptable, due to high incidence of specific adverse events. Further investigation is required for developing effective and acceptable and friendly specific therapies of ADPKD.

S t r e s z c z e n i e

Autosomalna dominująca wielotorbielowatość nerek jest jednym z wrodzonych schorzeń przebiegających z tworzeniem się torbieli narządowych, wykazującym głównie nerkową manifestację kliniczną (powiększenie objętości nerek, bóle okolicy lędźwiowej, krwiomocz, nadciśnienie tętnicze i niewydolność nerek). W niektórych przypadkach występują także objawy pozanerkowe, w postaci obecności torbieli wątroby, tętniaków naczyń mózgowych i aorty oraz uchyłków jelita grubego. Tło genetyczne jest skutkiem mutacji genów *PKD1* i *PKD2*, które kodują swoiste produkty białkowe, znane jako policystyna 1 i 2. Niewydolność nerek przede wszystkim rozwija się w 6. dekadzie życia. Niezależnie od tradycyjnego postępowania zachowawczego stosowanego w przewlekłej chorobie nerek, podejmowane są próby stosowania (w ramach badań klinicznych) celowanej terapii ukierunkowanej na wybrane elementy patomechanizmu tej choroby, zawierające wykorzystywanie inhibitorów konwertazy angiotensyny (ACE), blokerów szlaku mTOR, receptorów dla wazopresyny (V2) oraz inhibitorów cAMP. Żaden z tych sposobów leczenia nie okazał się jednoznacznie skuteczny w zakresie zahamowania powstawania i powiększania się torbieli jednocześnie z powstrzymaniem postępu niewydolności nerek bądź też częstość i nasilenie objawów niepożądanych były zbyt duże. Nadal konieczne jest prowadzenie kolejnych badań, mających na celu stworzenie skutecznej, ale jednocześnie akceptowalnej klinicznie terapii autosomalnej dominującej wielotorbielowatości nerek.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is hereditary cystic disorder with predominantly renal manifestation (large kidneys, flank pain, haematuria, hypertension and renal insufficiency). Overall incidence adult population is 1/500-1/1000. Renal cysts are localized in all nephron segments (1). Ultrasonography (USG) is a major screening diagnostic tool and Ravine criteria are very simple and effective in preliminary diagnosis, as presented in table 1 (2). Arterial hypertension may precede the development of chronic kidney disease, as independent factor, re-

lated to renal volume and number of renal cysts. There is variable incidence of extrarenal comorbidities, including vascular wall pathologies localized in brain or aorta, prolapse of mitral valve, development of hepatic cysts and colonic diverticula. The overall incidence of specific symptoms and comorbidities of ADPKD is presented in table 2 (3-5). These data clearly show, that the age of the patient and longer duration of the disease are crucial to develop relevant overt symptoms and they are present more frequently in adult than in pediatric cases. Similar time correlation is relevant to the development of chronic kidney disease and then end-stage renal failure. To some extend it depends on gene mutation, as in *PKD1* the end-stage renal failure develops about one and a half of the decade earlier, than in *PKD2* mutation; (mean 53 vs 69 years), which probably is related to the final number of developing cysts, however in general the renal function is stable within first 40-50 years of age (when the cysts develop and grow) and then, in the stage of inflammation and fibrosis of renal parenchyma, the chronic renal disease accelerates and patients loose the GFR beyond the age of 50 (1, 6-9). This is related to the final cysts growth and cumulated, final kidney volume (10). The dynamics of this process is presented in figure 1 (9).

Table 1. Ravine ultrasonographic criteria for screening the ADPKD (2).

Age (years)	Positive family history	Negative family history
< 30	2 cysts bilaterally or unilaterally	5 cysts bilaterally
30-60	4 cysts bilaterally	5 cysts bilaterally
> 60	8 cysts bilaterally	8 cysts bilaterally

Table 2. Clinical manifestation including extrarenal comorbidity of ADPKD in adults and children (3-5).

Symptom	ADPKD in adults (% of cases)	ADPKD in children (% of cases)
Haematuria	35-50	10
Urine concentrating defect	100	60
Proteinuria	18	14
Nephrolithiasis	20	Not known
Flank/abdominal pain	60	10
Hepatic cysts	83	Up to 55
Colonic diverticula	82	Not known
Cerebral aneurysms	5-7	< 5
Prolapse of the mitral valve	26	12
Hypertension preceding loss of renal function	60	22

EXTRARENAL SYMPTOMS IN ADPKD PATIENTS

Liver cysts and intestinal diverticula

There are two major types of liver cysts – one, related to ADPKD and *PKD1*/*PKD2* genes mutations, with prevalence of 0.2% and the second, rare isolated polycystic liver disease (prevalence < 0.01%), related to distinct (from ADPKD) gene mutation (gene *PRKCSH*; encoding hepatocystin). Similarly as in ADPKD, advancing age of the patient is a risk factor for liver – cyst growth and dysfunction (11). Colonic diverticula are quite common in adult ADPKD patients, however they are mainly asymptomatic. In cases of inflammation (diverticulitis) they become very severe clinical problem with high mortality rate (12). This pathology may be also localized in duodenum (13).

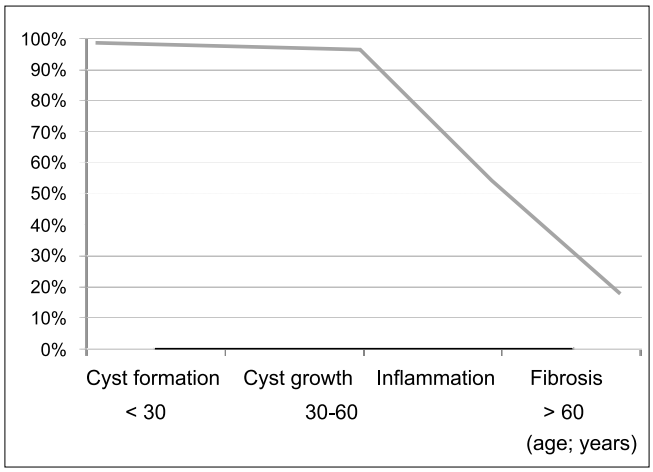

Fig. 1. Deterioration of GFR (% from baseline) in course of ADPKD.

Vascular pathology in ADPKD

There is increasing evidence that normal local expression of ADPKD gene products – *PKD1* and *PKD2* in vascular endothelium and smooth muscle is important for vessel wall structure, stability and function (14, 15). From clinical point, the vascular anomalies reported in ADPKD patients include mainly intracranial aneurysms and pathology of aorta. It should be stressed, that not all mutations of *PKD1* gene are definitely pathogenic for intracranial aneurysms, anyway, as reported by Else-Kröner-Fresenius Registry for ADPKD – there are also high specific mutations (such as 964 C/T), which allow for identification of the patients at high risk (16). The study from China, screening overall 355 patients with ADPKD for intracranial aneurysms showed, that overall incidence was 12.4%, the majority of confirmed cases was at age between 50-69 years and interval between diagnosing ADPKD and presence of aneurysms was 12.2 years. The family history for haemorrhagic stroke was positive in about 1/4 of confirmed cases (17). The majority of aneurysms were localized in internal carotid, middle cerebral or anterior communicating arteries and were mainly of 3-5.9 mm diameter. Another vascular pathology in ADPKD is dissecting aortal aneurysm. The animal model (*PKD1* hypomorphic mice) of aneurysm formation shows sequential process of: accumulation of excess of matrix components between elastin lamellae, detachment of endothelial cells from lamellae, and increase of intima cells. The combination of weak aortic media and the tear in the intima, leads to partial rupture of the vascular vessel and intramural bleeding (18). The presence of aortic aneurysms in

ADPKD patients was reported from decades, showing increasing incidence with age (> 40 years) and localization in both abdominal or thoracic aorta. There was no correlation with gender or end-stage renal failure, neither with arterial hypertension (19-23).

Targeted pharmacotherapy of ADPKD

Several clinical trials have been conducted in ADPKD patients, aiming to slow both the growth rate of renal cysts (and consequently to slow the increase of the total renal volume) and the decrease of glomerular filtration rate. The targets of specific drugs were among several pathways of the disease mechanism and in clinical setting included use of ACE, mTOR, V2 receptor and cAMP inhibitors. The range of therapeutic targets and drugs is presented in figure 2 and details of the selected major clinical trials are described in table 3.

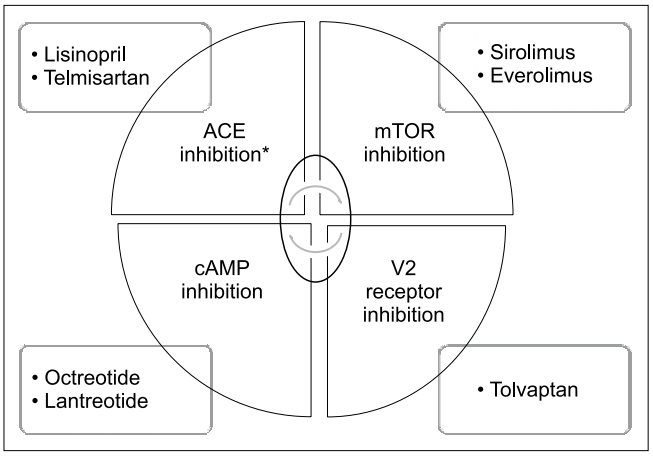

Fig. 2. Targets for pharmacotherapy in ADPKD.
*Only in terms of slowing the decline of GFR

The effect of mTOR inhibition was disappointing, as sirolimus showed no effect at all, and everolimus slowed the growth of the total kidney volume, however did not slow the rate of renal function decline (24, 25). There have been some later comments of prominent clinicians in regard to these results, suggesting that the dose of sirolimus used in this trial (2 mg/d) was "too low" and everolimus was used "too late" in terms of GFR entry criteria (mean in enrolled patients: 53 ± 19.8 ml/min) (26), however these suggestions were not further tested in practice. Inhibition of V2 receptors by tolvaptan was evaluated in another clinical trial. The results "per se" was positive, as tolvaptan slowed both the increase in total kidney volume and decline of renal function over 3-years, however therapy was associated with high discontinuation rate (about 30%) due to not tolerable adverse drug-related events such, as tremendous thirst, polyuria, nocturia, dry mouth and polydipsia (27). Another important aspect was the cost of therapy, as monthly cost of the drug was 5760 USD, which has given additional cost of 744 100 USD per QALY gained compared to standard care (28). Another pathway inhibition (cAMP) was tested with use of long acting somastatin analogue – octreotide administered as intramuscular injections. The effect on increase of kidney volume was positive within first year and then disappeared. The effect on slowing the decline of GFR was maintained during 3 years of follow-up. Angiotensin blockade was used in ADPKD in purpose limited to slow the decline of GFR. The composite primary outcome was the time to death, end-stage renal disease or a 50% reduction from baseline eGFR. The baseline eGFR in two groups (lisinopril/termisartan and lisinopril/placebo) was 48.5 ± 11.5 and 47.9 ± 12.2 ml/min, respectively. There was no significant difference between the study groups in the incidence of the composite primary outcome, as well as incidence of adverse events (30).

Table 3. Major clinical trials in ADPKD (24, 25, 27, 29, 30).

Name of the trial Tested drug	Entry criteria: Age (years) GFR (ml/min)	Number of patients Duration (months)	Effect on cysts growth Effect on – Δ GFR Comment
SUISSE ADPKD Sirolimus	18-40 > 70	100 18	Not significant Not significant Specific drug-related adverse events
Everolimus in ADPKD	18-65 30-90	400 24	Positive, significant Not significant Everolimus slowed the increase of total kidney volume, but did not slow the progression of renal impairment Specific drug-related adverse events
TEMPO Tolvaptan	18-40 > 70	417 36	Positive, significant Positive, significant Specific, drug-related adverse events were not acceptable for about 1/3 of the patients, who withhold the treatment The cost of the drug was very high (5760 USD/month)
ALADIN Somatostatin	> 18 > 70	66 36	Positive, significant within first year, than the effect disappears Positive, significant Drug given intramuscular Acute cholecystitis and cholelithiasis in some cases as adverse event was present
HALT-PKD A Lisinopril/Telmisartan vs Lisinopril/placebo	18-64 25-60	548 48	The composite primary outcome was the time to death, end-stage renal disease or a 50% reduction from baseline eGFR There was no significant difference between the study groups in the incidence of the composite primary outcome

CONCLUSIONS

1. Autosomal dominant polycystic kidney disease is associated with significant extrarenal comorbidities, including severe vascular and hepatic abnormalities, related to common genetic background, therefore ADPKD patients, especially beyond 50 years of age, should be screened for these pathologies.
2. Several trials have been conducted to verify the efficacy and safety of numerous target-specific drugs, aimed to slow the rate of increase of the total kidney volume and the rate of decline of renal function.
3. The results of these trials were not universally optimistic, or due to lack of efficacy, uncertainty of drug dosing, variable entry criteria (in regard to baseline GFR), drug toxicity or overall cost. Further attempts are required to elaborate the optimal care of ADPKD patients.

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