REVIEW ARTICLE

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Recent trials in autosomal dominant polycystic kidney disease

Ensaios recentes na doença poliquística renal autossómica dominante

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ABSTRACT

After two decades of major achievements in the understanding of genetics and pathophysiology of autosomal dominant polycystic kidney disease (ADPKD) several Stage III randomized and controlled clinical trials involving thousands of patients had the results published recently. In this article, the authors review the results of the major clinical trials discussing the clinical outcomes, adverse effects and limitations as well as the future directions in this exciting investigation.

Key-Words: ADPKD; clinical-trials; octreotide; sirolimus; tolvaptam.

RESUMO

Após duas décadas de intensa investigação no domínio da genética e da fisiopatologia da doença poliquística renal autossómica dominante foram publicados os resultados de alguns ensaios clínicos aleatorizados e controlados envolvendo milhares de doentes. Neste artigo os autores revêm e discutem os resultados clínicos, os efeitos adversos e as limitações destes estudos bem como antevêm as futuras linhas de investigação neste domínio.

Palavras-chave: DPRAD;ensaios-clínicos; octreotido; sirolimus; tolvaptan.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most prevalent monogenic disorders in adults and is responsible for about 8-10% of patients with end-stage kidney disease requiring renal replacement therapy worldwide[1]. So far, the management of ADPKD patients has been based on non-specific measures, such as blood pressure control, use of ACE inhibitors, low-salt diet, high water intake and protein restriction, in order to slow the decline of renal function and to promote cardiovascular protection[2]. In the last decade, however, the growing understanding of molecular mechanisms beyond ADPKD, identified possible targets for therapeutic intervention[3]. New therapies that act directly on cyst growth, such as vasopressin receptor antagonists[4-6], somatostatin analogues[7-9], and mammalian target of rapamycin (mTOR) inhibitors[10], have been studied with promising results.

Mutations on PKD1 and PKD2 genes are responsible for most cases of ADPKD[11, 12]. The PKD1 and PKD2 genes encode polycystin-1 and polycystin-2, respectively, which are glycosylated integral membrane proteins present in plasma membrane and cilia of the renal tubular epithelia and other sites of cyst growth in ADPKD, such as hepatic bile ducts and pancreatic ducts[13, 14]. Polycystin-1 is an adhesion molecule thought to be involved in cell-cell and cell-matrix interactions, while polycistin-2 is similar to a voltage-gated calcium channel. Both proteins interact to regulate cellular calcium influx[14].

The mechanisms involved in cystogenesis are not fully understood, but disruption in cilia structure has been proved to be a major event in cyst formation[15] and derangements in cyclic AMP (cAMP) secondary to changes in intracellular calcium, have been demonstrated to be an important factor responsible for cell proliferation and fluid secretion leading to cyst enlargement[16].

Progressive cyst formation and growth over the years lead to development of hypertension, chronic kidney disease and other complications, such as flank pain and haematuria secondary to cyst haemorrhage, calculi and urinary tract infection[3].

Considering all these pathological mechanisms that induce severe alterations in kidney's architecture and ultimately drive to renal failure, it seems logical that an intervention that stops or slows cyst growth may be beneficial in the outcomes of patients with ADPKD. However, one of the major constraints of the interventional studies in ADPKD is the way to evaluate progression. In fact, clinically significant loss of renal function occurs late in the natural history of the disease. It became evident that cysts size and number and overall kidney volume increase early in the evolution of the disease. The CRISP study (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease)[17] evaluated 241 patients with ADPKD, measuring the annual rate of change of kidney volumes in a three-year follow-up study. The CRISP investigators found that total kidney volume increased exponentially and was associated with deterioration of renal function over time. Moreover, increased renal volume is observed as early as in childhood and precedes any clinically significant loss of renal function[18]. Therefore, measuring kidney volumes emerged as the most important surrogate marker of progression of chronic renal failure in ADPKD. Now, scientists worldwide were able to test different approaches to sustain the progressive nature of the disease comparing the rate of growth in kidney size in each arm of the clinical trial.

On the other hand, significant advances in the pathophysiology of ADPKD from gene to cellular level pointed to the fact that protein product of the PKD1 gene and PKD2 gene are involved in several functions at the cellular level, such as ciliary function, aberrant intracellular calcium signaling, increased cyclic-AMP and regulation of cell cycle through mTOR pathway. Targeting to these functions was an obvious way to alter the natural history of cyst formation and animal models of PKD were used to test a variety of drugs that interfere in the pathway of cyst formation. Drugs that were previously used in humans for other reasons, such as mTOR inhibitors in renal transplantation or somatostatin analogues for neuroendocrine tumours were firstly tested for obvious reasons.

The aim of this article is to review the most recent clinical trials, whose results were published recently in the literature involving a substantial number of patients with ADPKD and several centres worldwide.

SOMATOSTATIN ANALOGUES

Somatostatin is a cyclic 14 aminoacid peptide secreted by pancreatic islets, gastrointestinal tract, nervous system and thyroid gland thought to inhibit adenylyl cyclase and post-cAMP events[19]. Several somatostatin analogues have been described, including octreotide[20]. Five somatostatin receptors have been cloned and were named sst1 to sst5. The sst2 receptor, which shows high affinity for octreotide is expressed in proximal and collecting tubules and also in medullary vasa recta[21]. In animal models, octreotide lowered cAMP levels in cholangiocytes and serum, slowing liver and kidney disease progression[22].

Considering cAMP role on fluid secretion and cyst growth, some authors hypothesized that somatostatin and its analogues, by means of cAMP inhibition, could have a beneficial effect retarding kidney enlargement and renal insufficiency in ADPKD. In 2005, Ruggenenti and co-workers[9] performed a pilot randomized, cross-over, placebo-controlled trial to compare the risk/benefit profile of long-acting somatostatin (octreotide–LAR) or placebo in adult patients with ADPKD. After a 6-month period, in the 12 patients that concluded the study, the percentage of kidney volume increase was significantly lower on octreotide-LAR (2.2% vs. 5.9%, $p < 0.05$), but there was no significant change in glomerular filtration rate (GFR) in both groups. The drug was well tolerated in general, with one case of asymptomatic cholelithiasis, three cases of watery diarrhoea and one case of mild increase in alanine aminotransferese levels. All resolved spontaneously after few months. This work showed that octreotide-LAR is effective in slowing cyst growth when compared to placebo, with a good safety and tolerability profile. The GFR was not different between groups, but these results must be interpreted taking into consideration, both the short follow-up and also the effect of octreotide in decreasing GFR, probably by inhibiting the growth hormone and, thus, reducing glomerular and tubular hypertrophy of the residual nephrons[23, 24].

Similar findings were obtained by van Keimpema *et al.*[25], in a randomized, double-blinded, placebo--controlled trial designed to assess the effect of lanreotide (a somatostatin analogue with lower affinity for the sst2 receptor than octreotide) versus placebo in liver volume. After one year, the authors found a decrease by 1.5% in kidney volume in the lanreotide group, while there was an increase by 3.4% in the placebo group. Despite the promising results, we must consider that among the 54 patients enrolled, only 32 had ADPKD, and only 12 (37.5%) of those received lanreotide.

Later, in 2010, Hogan *et al.*[8] designed a randomized (2:1), double-blinded, placebo-controlled trial of octreotide-LAR vs. placebo. The primary end point was change in liver volume and secondary end points included change in kidney volume and changes in GFR after one year of treatment. Of the 42 patients who underwent randomization, 13 were excluded for kidney analysis due to presence of polycystic liver disease without kidney involvement or previous renal transplantation. The authors had similar results, finding a significant smaller increase in kidney volume in the octreotide-LAR group after one year (8.61% vs. 0.25%, $p = 0.045$), but no significant change in GFR. The quality of life, evaluated by physical activity and body pain were significantly better in the octreotide-LAR group. In this trial, 18 patients suffered gastrointestinal side effects, some of them were managed with dose reduction, but none was withdrawn from the study.

To better clarify the role of octreotide in cyst growth in a long-term fashion, Hogan *et al.*[26] performed an open-label extension of a previous study[8] for one additional year, completing a total follow-up period of 2 years. In this year extension, all patients were treated with octreortide, independently of their previous assignment. The results showed that octreotide inhibited renal enlargement during the first year of treatment in patients always treated with octreotide, and in the second year in the patients that were initially treated with placebo, but not throughout the second year in the group always treated with octreotide. There was no difference in GFR between groups and the treatment was relatively well tolerated for 2 years.

Recently, the effect of a long-acting somatostatin on dIsease progression in nephropathy due to autosomal dominant polycystic kidney disease (ALADIN) trial[7], analysed the change in kidney volume at 1 year and 3 years follow-up in 79 patients. This multicentre, randomized, single-blinded, placebo--controlled, parallel-group trial is the largest and with longer follow-up comparing octreotide-LAR with

placebo. Seventy-three patients (37 octreotide-LAR, 36 placebo) completed the 3-year study. After the first year of treatment, the increase in kidney volume was significantly less in the octreotide-LAR group compared to the placebo group (p = 0.032); but, after 3 years, the increase in kidney volume was numerically smaller in the octreotide-LAR group than in the placebo, but not statiscally significant. Possible explanations for these results are somatostatin receptors down-regulation or initial cyst shrink followed by stabilization during the follow-up. Short-term GFR reduction was the same between both groups in the first year, but subsequent decline in GFR from year 1 to 3 was slower by almost 50% (p = 0.03) in octreotide-LAR. In their discussion, the authors suggest that patients on octreotide-LAR, despite a non-significant decrease in GFR during the first year, exhibit a long-term better preservation of GFR, probably by reducing maladaptative glomerular and tubular hypertrophy. Again, on this study octreotide-LAR was well tolerated. Four cases of biliary tract disease and 14 cases of diarrhoea were reported, but those patients were not withdrawn from the study.

A larger randomized trial, DIPAK study 1, is currently active, planning to enroll 300 adult patients[27] in order to better disclosure the effects of lanreotide in GFR.

In summary, although all these independent trials have shown encouraging results on changes in kidney and liver volume, better quality of life and a good safety and tolerability profile, all of them are limited by small sample sizes and short term follow-up. The largest trial, so far performed to assess the effect of somatostatin analogues in kidney volume, the ALADIN trial[7], in contrast to the previous studies, showed promising results in slowing the decline on GFR in a long-term fashion. Larger and longer trials are still necessary to better establish the role of these drugs in the treatment of patients with ADPKD.

ARGININE VASOPRESSINE V2 RECEPTOR ANTAGONISTS

Arginine vasopressine (AVP) influences salt and water transport in renal epithelia, mainly through V2 receptors, which are preferentially located in medullary thick ascending limb, connecting tubules and collecting ducts in both humans and animal models[28, 29]. The ADPKD patients exhibit increased circulating levels of AVP[30], which is the main agonist of adenylyl cyclase in collecting ducts[31] and, thus, a power modulator of cytogenesis. Several animal models have shown that AVP V2 receptor antagonists OCP-31260 and tolvaptan have protective effects in the development of renal cysts by lowering renal cAMP levels and down regulating the expression of V2 receptors[29, 32-34]. Arginine vasopressine V2 receptor antagonists may also be beneficial in blood pressure control and chronic kidney disease progression[35, 36].

Irazabal *et al.*[5] performed a single centre study with 20 ADPKD patients treated with split-dose regimen of tolvaptan for 1 week, in order to assess the short-term effects of this AVP V2 receptor antagonist on renal function and kidney volume. The authors found that tolvaptan induced aquaresis, which was accompanied by 1.6% reduction in body weight, 8.9% increase in serum creatinine and 8.6% reduction in GFR. These findings were not associated with significant changes in renal blood flow but probably are due to effects on tubuloglomerular feedback and/or glomerular ultrafiltration. In a *post-hoc* analysis, kidney volume was analysed and the authors reported a 3.1% significant decrease in kidney volume at the end of one-week treatment. Also, this percentage was higher in patients with GFR › 60mL/min/1.73m^2. Based on these results, the authors concluded that tolvaptan had a positive short-term effect in reducing kidney volume and hypothesized that it could promote better results if used with higher GFR, earlier in the course of the disease.

But if the hypothesis of a long-term treatment with tolvaptan in ADPKD patients is generated, it must be studied considering efficacy, safety and tolerability, in larger samples and for longer follow-up. In Irazabal and co-workers study (21544064)[5], all patients experienced polyuria and polydipsia, and most of them had nocturia. Although these adverse events were not severe enough to cause study discontinuation in a short-term follow-up, the same was not observed in longer follow-up studies.

Higashihara *et al.*[4] performed an analysis of two 3-years studies of tolvaptan in 63 adult ADPKD patients randomly matched 1:2 to historical controls, in order to establish its safety, tolerability and efficacy. Subjects with GFR ‹ 30mL/min/1.73m^2 were

excluded. A split-dose regimen of tolvaptan was administred and up-titration was done until tolerability was reached. Fifty-one patients (81%) completed 3 years of treatment with tolvaptan and presented a significant smaller increase in kidney volume when compared to matched controls (1.7% vs. 5.8%, $p < 0.001$). Annual decrease in GFR was also smaller in tolvaptan-treated patients (-0.71ml/min/1.73m^2 vs. -2.1mL/min/1.73m^2, $p = 0.01$). All tolvaptan-treated patients suffered adverse events, mostly mild to moderate; however, six out of the 12 patients that abandoned the study, did so because of the adverse events. These long-term results seem promising, but the study was limited by the small number of patients and non-contemporary controls who were, in a large percentage, not ethnic-matched with the tolvaptan--treated patients.

The largest study, performed so far, analysing the effect of tolvaptan in ADPKD (TEMPO 3:4 trial)[6], assigned 1445 adult ADPKD patients with a GFR ≥ 60mL/min/1.73m2 and a total kidney volume ≥ 750mL. In this phase 3, multicentre, double-blinded, placebo-controlled, 3-year trial, patients were randomized 2:1 for tolvaptan in a twice-daily regimen versus placebo. Three different doses of tolvaptan were used, according to the tolerability. The primary end point, annual rate of change in total kidney volume, was increased by 2.8% per year in the tolvaptan group, while it increased by 5.5% per year with placebo ($p < 0.001$). The larger effect was observed in the first year of treatment and tolvaptan showed a beneficial effect on kidney volume in all subgroup analyses (gender, age, kidney volume at baseline, GFR at baseline and hypertension status). The results on secondary composite outcome (worsening of renal function, kidney pain, hypertension and albuminuria) also favoured tolvaptan with 44 vs. 55 events per 100 follow-up years, $p = 0.01$. Slope of kidney function, assessed by the reciprocal of serum creatinine, was better with tolvaptan (-2.61mg/mL^{-1} vs. -3.81mg/mL^{-1}, $p < 0.001$). Similarly to a previous study (21903984)[4], adverse events where very frequent and affected more than 97% of the patients in both groups. Tolvaptan-treated patients experienced mainly aquaresis-related adverse events and elevation of liver enzymes, while the placebo group more often suffered ADPKD-related adverse events. A higher trial discontinuation was observed in the tolvaptan group (23% vs. 13.8%) overall but also if the study was discontinued due to adverse events (15.4% vs. 5.0%). This large trial and those smaller previous ones are unanimously showing smaller increases in kidney volume when patients are treated with AVP V2 receptor antagonists. These findings are encouraging since kidney volume is a prognostic biomarker in ADPKD[137]. However, adverse events were frequent and limited treatment in some patients. Furthermore, questions related with tolvaptan costs[38], awareness of the elevation in creatinine after treatment initiation, its reversibility and indications for treatment interruption, are still unanswered[39]. On the other hand, cyst complications are more frequent in non-treated patients, representing also adverse events and affecting quality of life. The benefits and risks of tolvaptan must be taken into consideration in long-term management of ADPKD patients.

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS (MTOR INHIBITORS)

The mTOR is a serine/threonine protein kinase that regulates cell growth, proliferation, motility and survival and it is also involved in protein synthesis and transcription. It belongs to the phosphatidylinositol 3-kinase-related kinase protein family. The activity of mTOR kinase has been shown to be involved in the proliferation and enlargement of the cystic epithelium, in animal models with ADPKD; therefore, it seams reasonable that mTOR inhibitors theoretically should delay cystic formation and growth, retarding the progression of kidney disease. There are two known mTOR inhibitors, sirolimus (rapamycin) and everolimus. Sirolimus is a macrocytic triene antibiotic, produced by fermentation of *Streptomyces hygroscopicus*. It was discovered in the soil of Rapa Nui. Everolimus is as analogue of sirolimus. Both molecules bind to FK binding protein, modulating the activity of mTOR, resulting in cell cycle arrest. Because of their immunosuppressive and anti proliferative properties, they are used in kidney and liver transplant and in proliferative diseases, as tuberous sclerosis complex (TSC) and malignancy. These molecules are metabolized by the liver and excreted mainly in the faeces. The main side effects are haematologic (anaemia, leucopenia and thrombocytopenia), although many others are described like diarrhoea, nausea, and hypercholesterolemia. Sirolimus and everolimus are currently under study in

ADPKD, in animal models and humans, with somewhat conflicting results.

The effect of rapamycin was studied in a rat model, by Tao *et al*. The proliferation of tubular cells, cyst formation and renal failure were evaluated. The authors describe that, after five weeks of therapy, in the mice subjected to inhibition of the mTOR, there was less proliferation of the tubular cells and inhibition of cystogenesis and kidney enlargement[40]. Another study in rats, conducted by Wahl *et al*., also concluded that treatment with sirolimus retarded cyst development and delayed the loss of renal function. This trial was done in a small group of 5-week-old rats that were treated for 3 months[41]. The trials in animal models were small and had short follow-up periods, but the positive results stimulated the design of several clinical trials.

Stallone *et al*.[42] conducted a prospected randomized study to evaluate the effects of rapamycin in the evolution of type 1 ADPKD (The RAPYD-study). Fifty-five patients were randomized to receive ramipril (group A), ramipril plus high-dose rapamycin (group B: trough levels of 6-8ng/ml) or ramipril plus low--dose rapamycin (group C: trough levels of 2-4 ng/ml). All patients had an estimated GFR between 40 and 80 ml/min/1.73m^2, evaluated by the MDRD formula. The primary objectives of the study were to evaluate if rapamycin could reduce the progressive increase in single cyst and total kidney volume, the rate of the decline in renal functional and to identify the optimal rapamycin dose. The cyst and kidney volume was evaluated by magnetic resonance imaging at baseline and at 24 months of initiation of drug therapy, and the groups had no statistically significant differences at baseline. Measuring the p70 phosphorylation in peripheral blood mononuclear cells, a direct downstream target of mTOR, was used to monitor the efficacy of rapamycin. At 24 months, the authors did not observe any significant difference in change of total kidney or cystic volume among the three study groups. Also, the changes in the estimated creatinine clearance were not significantly different after 24 months of treatment. In the end of the trial, groups B and C presented an increase in urinary protein excretion compared with group A (the increase was higher in group B).

The use of sirolimus was also evaluated by the group of Perico *et al.*[10], in the SIRENA study. SIRENA was a randomized crossover study, comparing a 6-month treatment with mTOR inhibitor sirolimus and conventional therapy alone. Like in the study conducted by Stallone *et al*., individual cyst and total kidney volume was evaluated by magnetic resonance imaging. This was a small study, with 21 patients enrolled but only 15 completing the follow-up (all of them with a GFR superior to 40ml/kg/1.73m^2). In the end of the 6-month period, the patients treated with sirolimus showed stabilization of the cystic volume and an increase in renal parenquimal volume, compared with the group under conventional therapy. Thus, this study suggests that therapy with sirolimus halted cyst growth and increased parenchymal volume, but whether these effects correlate with improved long-term outcomes is still unknown. Of notice, the urinary albumin excretion rate was higher in the sirolimus group.

Serra *et al*.[43], from the University of Zurich, also analysed the effect of sirolimus versus standard care in the variation of kidney volume over time. This study was an open-label randomized trial and was larger than the previous ones. A total of 100 patients were enrolled, followed for 18 months. All patients had an estimated creatinine clearance of at least 70ml/kg/1.73m^2. Total kidney volume was evaluated by magnetic resonance imaging. At the end of the study, no statistic significant difference was detected between the two groups, suggesting that treatment with sirolimus did not halt cystic growth. As in the previous two trials, proteinuria increased in the group under sirolimus, compared with the group treated with standard care.

Everolimus was also studied against placebo, in a larger number of patients[44]. In this double-blind controlled trial, 433 patients with ADPKD were assigned to receive everolimus or placebo. Total change in total kidney volume was evaluated by magnetic resonance imaging at 12 and 24 months. In the end of the two-year period, compared to placebo, everolimus slowed the increase in total kidney volume, but did not slow the progression of kidney disease.

Side effects were reported in all clinical trials, mainly haematologic and gastrointestinal, but in general they occurred in a small number of patients and were mild or moderate. The patients treated with mTOR presented an increase in urinary protein

excretion, compared with the patients treated with standard care.

In spite of the benefits showed in animal models, to date the clinical trials conducted in patients with ADPKD failed to demonstrate benefit, in the short term, in the progression of kidney disease. To determine if the stage of renal disease and the tissue concentrations of the mTOR were key issues in this results, a study was conducted, in an animal model, by Novalic *et al.*[45]. They studied the effects of low (3ng/ml) versus high (30-60ng/ml) dose sirolimus in different stages of kidney disease in an animal model. Only the group treated with high dose sirolimus and early in disease course showed inhibition of cystogenesis and accelerated cyst regression. In this group, there were hardly any tubular dilatations and renal tissue architecture appeared almost unaffected, whereas in the untreated group mild dilations and small cortical cysts were detected. Higher doses of mTOR inhibitors will probably translate in a higher rate of side effects. To evaluate this question, Shillingford *et al.*[46] studied the kidney-targeted delivery of a folate-conjugated form of rapamycin in rodents. The use of the folate-conjugated rapamycin molecule translated in a selective inhibition of the mTOR in the kidney, with significant attenuation of the proliferation and growth of renal cysts. This selective molecule is expected to exhibit reduced toxicity but it may induce unexpected effects if used in children, because folate is required for DNA synthesis by rapidly dividing cells.

Taken together, the evidence seems promising, but more studies are needed, enrolling a larger number of patients and longer follow-up, to determine the benefits of mTOR inhibition in ADPKD.

CONCLUSION

Although the results of the tolvaptam trial demonstrated a small benefit, the adverse effects and the number of dropouts is a matter of concern as therapy for ADPKD is anticipated as long-life intervention. Overall the results of these trials were disappointing as they did not confirm the expectations that emerged with the results in animal models. Further analysis of the population involved in clinical trials in ADPKD revealed that the rate of progression varies considerably among patients meaning that a better selection of the patients to include only those with rapid progression will make a difference[47].

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