

# Therapeutic advances in polycystic kidney disease: at the dawn of a new era

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## ■ INTRODUCTION

Polycystic Kidney Disease (PKD) is one of the most common hereditary diseases in humans, accounting for almost 5-10% of subjects on renal replacement therapies<sup>1</sup>. Although clinical symptoms occur most frequently in adult life, the hereditary nature of PKD has permitted the screening of first degree relatives and therefore to reach a diagnosis in early adulthood. That said, early diagnosis *per se* does not contribute to halting the progressive nature of the renal failure as no specific therapies are available as of yet. To date, therapeutic interventions in PKD are based on blood pressure control, protein restriction, avoidance of nephrotoxics and other nephroprotective measures. Although not specifically directed to PKD patients these interventions have contributed to better outcomes in recent years<sup>2</sup>. As cardiovascular disease is the most important cause of death in PKD and hypertension is the main risk factor for cardiovascular events, early diagnosis is required to screen for hypertension and this may contribute to reducing the rate of cardiovascular events in this population<sup>3</sup>.

As the result of intense investigation in basic sciences that followed the discovery of the genes responsible for ADPKD, recent advances have thrown up several possibilities of therapeutic intervention in PKD that specifically interfere with the known pathophysiology of the disease<sup>4</sup>.

## ■ CONVENTIONAL THERAPY IN PKD

Clinically, PKD is characterised by progressive involvement of the kidneys with fluid-filled cysts. Cysts may also be present in other organs but it is the kidney involvement that determines most of the clinical symptoms in the early stages of the disease. Prevalence of hypertension in young adults is greater than in the age-matched control population<sup>3-5</sup>. Cerebral aneurisms and urologic symptoms, such as nephrolithiasis and haematuria, are common, but progressive renal failure is the main concern for patients and nephrologists.

Therapeutic intervention in PKD depends on the stage of the disease. In early stages, detection of hypertension, changing lifestyle, diet and preventive interventions of urologic symptoms are the cornerstones of the therapy. In families with clustering of aneurism rupture, screening for cerebral aneurisms using Angio-MRI may be adequate<sup>6</sup>. Genetic counselling is also appropriate in this pre-reproductive phase. In later stages, therapeutic interventions are directed to reducing the rate of decline in renal function, to controlling risk factors for cardiovascular disease and preparing for renal replacement therapies.

Several risk factors have been implicated in the progression of renal failure in ADPKD<sup>7</sup>, such as the type of mutation, hypertension, urologic symptoms and renal volume. As hypertension is the only risk factor that is modifiable by medical intervention, most

attention has been slanted towards ascertaining whether control of hypertension will affect the progressive nature of the disease. The first interventional study to address the effect of blood pressure control and low protein diet in the progression of renal failure of PKD patients was the Modification in Diet in Renal Disease (MDRD) Study<sup>8</sup>. While not specifically aimed at PKD patients, almost 25% of the subjects had PKD. However, a subgroup analysis revealed that neither tight blood pressure control nor low protein diet significantly reduced the rate of renal deterioration<sup>9</sup>. One of the main limitations of the study was that patients had moderate to advanced renal failure and were therefore less likely to benefit from the intervention during the 2.2 years of the trial. Moreover, the separation of the groups in terms of the achieved mean arterial pressure was less than adequate. Nonetheless, similar results were obtained in other studies, shedding concern on our ability to control this disease<sup>10,11</sup>.

At this point it was clear that if an intervention was to be of any use, it should begin in the early stage of the disease. As renal function was apparently well preserved until late stages, the question was which end-point should be used to compare the effects of a medical intervention in this disease. The answer comes from the Consortium of Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP study) which demonstrated that kidney volume resulting from the cysts' expansion correlates tightly with the decline of renal function. The study also demonstrates that the volume expansion is continuous and quantifiable<sup>12</sup>. It meant that an adequate surrogate marker of disease progression was found and should be used as a measurable end-point in future trials.

## ■ RECENT THERAPEUTIC ADVANCES IN PKD

A light at the end of the tunnel appeared in recent years when encouraging results were reported in animal models of PKD<sup>13</sup>. Taking the pathophysiological importance of the secretory function of the cystic epithelia, which is mediated by cAMP, into consideration, a vasopressin receptor antagonist reduced the rate of cystic development in animal models. Similarly, the use of octreotide, a somatostatin agonist

that reduces the levels of cAMP in cystic epithelial cells, also reduces the rate of volume progression in patients with ADPKD<sup>14</sup>. The observed increased rate of proliferation and hyperplasia in cystic pathogenesis prompted a different approach: rapamycin, a well-known anti-proliferative agent was used in animal models of PKD and the results were encouraging<sup>15</sup>. Several other therapeutic options have been studied in animal models although their application to clinical practice remains to be proven (Table I).

**Table I**

Drugs tested in animal models of cystic kidney disease

|   |
|---|
| Probucol                                |
| Lovastatin                              |
| Paclitaxel                              |
| MAPKK/MEK inhibitors (AG825)            |
| ErbB antagonists (EKI-785; EKI-569)     |
| Tyrosine kinase inhibitors (PDI 184352) |
| c-Src inhibitor (WY-606)                |
| Antisense oligonucleotide to c-myc      |

## ■ Vasopressin receptor antagonists

Cyclic adenosine-monophosphate (cAMP) is an intra-cellular second messenger that is implicated in the pathogenesis of cystic kidney disease<sup>16</sup> and therefore a logical target for drug therapy in PKD. In 2003, the group of Torres<sup>13</sup> reported the effects of an antagonist of the V<sub>2</sub> receptor of vasopressin, OPC 31260. The V<sub>2</sub> receptor of vasopressin mediates the production of cAMP in collecting duct epithelium; consequently, the use of OPC 31260 reduced the renal accumulation of cAMP in mouse models of Autosomal Recessive Polycystic Kidney Disease (PCK rat), nephronophthisis (pcy rat) and Autosomal Dominant Polycystic Kidney Disease. Further evidence of the role of vasopressin in cystogenesis was the demonstration that high water intake, which suppresses vasopressin, exerts a protective effect in PCK rat model of PKD<sup>4</sup>. A more potent and selective human vasopressin receptor antagonist, tolvaptan, has been tested in phase II trials with encouraging results<sup>17</sup>. Tolvaptan has a great advantage because it has been tested in other clinical situations such as heart failure<sup>18</sup> and hyponatraemia due to SIADH<sup>19</sup> and hepatic cirrhosis. No major adverse effects have been reported except for thirst and polyuria, well tolerated by patients<sup>20</sup>. Phase III trials are expected to start in the current year<sup>4</sup>.

## ■ Octreotide

Octreotide is a long-acting somatostatin analogue that was used in a small randomised controlled study, with a cross-over design, for reducing the rate of volume expansion in ADPKD patients<sup>14</sup>. Volume progression was assessed by CT scan and even with this limited population good results were observed. It has been shown that somatostatin, via sst2 receptor, inhibits intra-cellular cAMP production in several models of PKD. Interestingly, somatostatin also inhibits cAMP, fluid secretion and cell proliferation in the liver<sup>4</sup> which could be an option in patients with enlarged cystic disease of the liver.

## ■ mTOR inhibitors

Beyond fluid secretion in cysts, mediated by cAMP, increased cell proliferation is a hallmark of PKD<sup>21</sup>. Intracellular mechanisms mediating cell proliferation involves hamartin and tuberlin, products of the genes TSC1 and TSC2, the genes responsible for Tuberous Sclerosis. Cystic kidneys is a common finding in Tuberous Sclerosis. Both hamartin and tuberlin function as a GTPase activating protein that controls the activity of mTOR, the mammalian target of rapamycin. mTOR phosphorylates S6K1 and 4EBP1, proteins that migrate to nucleus, and consequently promotes cell growth and cell cycle progression.

It was shown in animal models that inhibition of mTOR by rapamycin, a well-known immunosuppressor agent used in transplantation and cancer therapy, reduces the rate of expansive progression of cystic kidneys<sup>22,23</sup>. In PKD patients with renal transplant treated with rapamycin, reduction of renal volume of the native kidneys has been demonstrated when compared to PKD patients not receiving rapamycin<sup>24</sup>. Several trials using rapamycin are now underway.

## ■ CONCLUSION

More than 20 years after the localisation of the putative gene for ADPKD in the short arm of chromosome 16 and after intense research in clinical and genetic settings, a promising specific therapy is now on the horizon. For those caring for patients and families with PKD this is definitely good news.

**Conflict of interest statement.** None declared.

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