Autosomal dominant polycystic kidney disease and mTOR inhibitors: the narrow road between hope and disappointment

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Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease characterized by the development of innumerable cysts in the kidneys and progressive renal dysfunction eventually leading to end-stage renal disease. In a number of cases, cysts can develop also in the liver and in the pancreas. Inheritance is autosomal dominant and is caused by single-dose mutations of either the gene PKD1 in chromosome 16 or PKD2 in chromosome 4. These genes encode respectively polycystin 1 and polycystin 2, two modular membrane proteins that regulate tubular and vascular development in the kidneys, liver, brain, and pancreas by assembling large signalling complexes and activating several signalling pathways [1].

A number of studies have outlined the role of the mammalian target of rapamycin (mTOR) in the pathogenesis of cysts. The mTOR is a serin–treonin kinase coded by the gene FRAP1, which integrates several signals from cytokines, hormones, and growth factors and coordinates the cell cycle and cell proliferation [2]. The mTOR is a catalytic subunit of two complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is the downstream effector of the phosphatidylinositol 3 kinase (PI3-k) cascade that provides the signal for cell proliferation in response to the above-quoted stimuli. A main regulator of the activity of mTORC1 is the complex hamartin–tuberin, two proteins coded respectively by the genes TSC1 and TSC2. A reduced expression of either of these proteins leads to hyperactivity of mTORC1 and cellular hyperproliferation. A typical example of a disease caused by abnormal regulation of mTORC1 is tuberous sclerosis. This syndrome, characterized by the formation of angiomyolipomas and hamartomas in different organs, is caused by mutations of TSC1 or TSC2, with consequent inactivation of hamartin or tuberin, uncontrolled activity of mTORC1, and formation of benign tumours [3].

A reduced activity of the complex hamartin–tuberin caused by the genomic deletion of PKD1 and/or the adjacent gene TSC2 with hyperactivation of mTORC1 can also be involved in the pathogenesis of ADPKD. Shillingford et al. [4] demonstrated an interaction between tuberin and polycystin 1 leading to an exaggerated expression of mTOR in the epithelial cells of cysts not only in two murine models of polycystic disease (PKD) but also in patients.
with ADPKD; moreover, mTOR activity is low in normal human kidneys, while it is strongly upregulated in renal cyst-lining epithelial cells. A role in the pathogenesis of ADPKD is played also by cAMP and IGF-1 that, through the mediation of PI3-k and other kinases, activate the kinase receptors Ras and Raf necessary for providing the signal for epithelial cell proliferation. Inhibition of Ras or Raf can abolish the proliferation of epithelial cells from subjects with ADPKD caused by mutation of PKD1 [5]. These data suggest that the inhibition of mTORC1 may reduce cystogenesis in PKD.

There are two commercially available drugs that can inhibit mTORC1, sirolimus, a macrolactone produced by Streptomyces hygroscopicus, and its derivative everolimus. These drugs are highly lipophilic and easily enter the cell membrane. In the cytoplasm, they bind to a protein called FKBP12. It is the complex drug/FKBP12 that interferes with the mediation of mTORC1 by inhibiting its kinase activity and causing cell arrest in the G1 phase [6]. Sirolimus and everolimus have been patented as immunosuppressive agents in organ transplantation, but several lines of evidence show that their anti-proliferative activity can be exploited for treating other diseases, including tuberous sclerosis [7], renal carcinoma [8] and neuroendocrine tumours [9].

Experimental studies support a possible benefit of mTOR inhibitors in PKD. A number of investigators determined the effect of sirolimus or everolimus in the Han:SPRD rat model of PKD [10–13]. Both treatment regimens ameliorated kidney function, preserved the glomerular-tubular connection, and reduced proteinuria. In these studies, in Han:SPRD rats, the mutated gene encoded for Samcystin, and the cysts were mainly of proximal origin, while in human ADPKD, the mutated genes are PKD1 and PKD2, which encode for different proteins and cysts that originated from all parts of the nephron. Shillingford et al. obtained a mouse model of PKD with aberrant mTOR activation, epithelial proliferation, apoptosis, and progressive fibrosis by mosaic deletion of PKD1. Even in this model, sirolimus reduced cyst growth, preserved renal function, inhibited epithelial cell proliferation, increased apoptosis of cyst-lining epithelial cells, and inhibited fibrosis [14].

Apart from inhibited cystogenesis, there is another potential mechanism by which mTOR inhibitors might interfere with progression of disease in ADPKD. Wei et al. [15] demonstrated that there is angiogenesis in ADPKD. This process may be necessary for cyst cells to grow and may be responsible for increased vascular permeability facilitating fluid secretion into the cysts. Angiogenesis is under the control of vascular endothelial growth factors (VEGF) which use the PI3-k family of kinases to stimulate the proliferation of endothelial cells [16]. By inhibiting mTORC1, the downstream effector of PI3-k, everolimus and sirolimus may also inhibit angiogenesis in ADPKD, an effect presently exploited in oncology [17].

Apoptosis is a pathologic feature of most experimental models of PKD and human ADPKD. Although the effects of mTOR inhibitors on apoptosis are conflicting, at least in Han:SPRD rats, the active form of caspases, the major mediators of apoptosis, and the number of apoptotic tubular cells in cystic and non-cystic tubules are decreased by mTOR inhibitors [18].

What about the safety and efficacy of mTOR inhibition in human ADPKD? The tolerability of sirolimus was tested in 25 patients who received sirolimus, 2 mg/day, and compared with that of 25 well-matched patients randomized to standard care. At Month 6, the mean glomerular filtration rate (GFR) did not change significantly. Haematological parameters were similar in both groups, except for a mild reduction of the mean corpuscular volume of erythrocytes in patients receiving sirolimus. Lipid levels were similar in both groups. Adverse events were transient and mild, and no grade 3 or 4 events occurred. The incidence of infections was similar in the two groups. However, mucositis was significantly more frequent in the sirolimus group (72% versus 16%) [19]. In a cross-over study, Perico et al. [20] compared a 6-month treatment with sirolimus or conventional therapy alone on the growth of kidney volume in 21 patients with ADPKD. Compared with pre-treatment, the post-treatment mean total kidney volume increased less on sirolimus than on conventional therapy, but no difference between the two treatments could be detected. Cyst volume was stable on sirolimus and significantly increased on conventional therapy. However, the design, the small size and the short follow-up of this study do not allow us to reach any firm conclusion about the protective effect of mTOR inhibition on renal function.

At the last ERA–EDTA Congress in Munich, Germany, the results of two trials on the use of mTOR inhibitors were presented and have been simultaneously published ahead of print in The New England Journal of Medicine. The conclusions of the authors were substantially negative. This changed the feelings of the attending nephrologists from hope to disappointment. Trying to clarify this important topic is therefore important, considering that ADPKD causes much distress to the patients and their families, and also increases the burden of health system organizations.

Serra et al. [21] assigned 100 patients with a creatinine clearance ≥70 mL/min to receive either sirolimus (2 mg daily) or standard care. The median total kidney volume increase, as assessed by magnetic resonance, over an 18-month period was similar in the two groups. These negative results may be explained, at least in part, by the slow progression of ADPKD in the enrolled population, which can render it difficult to find differences in a short time. Actually, the annual rate of growth in total kidney volume was <10%. Although the magnitude of kidney volume change is considered to be a good predictor of progression in patients with ADPKD [22], it has been pointed out that a long observation is needed to catch differences related to treatment [23], since ~10–20% of patients may display volume regression because of a spontaneous rupture of cysts [24]. In a 2-year, double-blind trial, Walz et al. [25] randomly assigned 433 patients with ADPKD to receive either placebo or everolimus. In comparison with placebo, everolimus slowed the increase in total kidney volume in patients with ADPKD particularly in the first year, while the decline in creatinine clearance was similar. This discrepancy may be accounted for by the large differ-
ence in the baseline GFR that ranged from 30 to 90 mL/min. As pointed out by Watnick and Germino [26], it is possible that in some patients, the disease was too advanced to yield a functional benefit, despite a reduction in renal size. In animals with initial parenchymal damage, mTOR inhibitors can inhibit glomerular hyperfiltration, glomerulosclerosis and interstitial fibrosis [27]. Instead, in the remnant kidney, they can inhibit the glomerular repair reaction and favour the progression to renal failure [28]. Similarly, after conversion from calcineurin inhibitors to sirolimus, renal function deterioration in patients with GFR <40 mL/min [29]. These opposite effects may be emphasized by the use of high dosage. In the model of anti-Thy-1 antiserum, low-dose everolimus protected renal function in rats with mild glomerular lesions, while high-dose everolimus increased glomerulosclerosis, crescent formation and mortality [30]. In this regard, it should be pointed out that patients enrolled in the study of Walz et al. not only had large differences in the baseline GFR but also showed large differences in the blood levels of everolimus that had to range from between 3 and 8 ng/mL. Unfortunately, neither in the study of Serra et al. nor in that of Walz et al., the rate of renal progression before starting treatment was available, so one cannot exclude an unbalanced randomization between fast and slow progressors. Moreover, both studies used as the primary outcome variable the total kidney volume, but no ADPKD patient starts dialysis on the basis of their total kidney volume. Probably, the evolution of renal function over time should be better. The interpretation of the results of these studies should also be re-evaluated by using the estimated GFR as the primary variable, given that the applied linear model of the estimated GFR decrease over time is not adequate at least in the first months of follow-up [26].

In conclusion, the therapeutic role of mTOR inhibitors in ADPKD is still uncertain. It is possible that these agents may slow the kidney volume enlargement and renal function deterioration in a subset of patients, while they can be ineffective or even harmful in other patients. Future trials should be addressed to identify the potential responders, the level of renal function at which to start therapy, and the optimal dose to use in patients with ADPKD.

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Baseline creatinine to define acute kidney injury: is there any consensus?

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Acute kidney injury (AKI) is an important clinical problem which is associated with higher mortality, increased health resource utilization and increased risk for chronic kidney disease (CKD) [1–3]. Previously, more than 30 definitions of acute renal failure have been used in the literature, resulting in a wide variation in reported incidence and mortality [4,5]. After the introduction of the consensus criteria Risk Injury Failure Loss End-Stage Renal Disease (RIFLE) [6] and Acute Kidney Injury Network (AKIN) [7,8], there has been a positive move towards the use of more standardized definitions in the literature. Despite their limitations, this has nevertheless been a step forward, allowing meaningful comparisons across studies [9].

The conceptual model of AKI is that of a rapid worsening of kidney function from pre-morbid levels. That said, ideally, a baseline serum creatinine (bCr) value which is reflective of the patient’s pre-morbid kidney function should be known, and this is the value to which we compare subsequent creatinine values to diagnose AKI. However, in many cases, bCr value is not readily available to the physician or research team [10]. When no information on prior renal function is available, the Acute Dialysis Quality Initiative has recommended back-estimation from the Modification of Diet in Renal Disease (MDRD) formula, assuming an estimated GFR of 75 mL/min/1.73 m² [6]. Various studies have used different ways to define the bCr, such as the creatinine at the time of hospital admission [11–13], the minimum creatinine value during the hospital stay [1,14,15], the creatinine estimated from MDRD [10,16–18] or the lowest value among these. The choice of bCr has a marked effect on the prevalence of AKI, the severity (or stages) of AKI and the mortality that is associated with AKI in various stages [9,19–22]. Moreover, such misclassification can lead to different therapeutic approaches, for example, being inappropriately aggressive in the case of false-positive AKI or misguided complacency in the case of false negatives.

The comparative merits of possible surrogate values for bCr, including MDRD estimation, have been addressed by a number of studies in both adults [19–21] and children [22]. The ideal way to ‘validate’ the use of estimated bCr (by MDRD) is to take an unselected cohort with known bCr (within the past year, ideally within the previous 3 months). Patients are then classified into RIFLE/AKIN classes based on both the known bCr and the estimated bCr. The misclassification that results from the use of the estimated bCr can then be quantified.

Bagshaw et al. performed a comparison of observed versus estimated bCr (by MDRD) for determination of RIFLE class in 1314 ICU patients [20]. Use of estimated bCr misclassified 18.8% of patients as having AKI on ICU admission. They concluded that estimated bCr appears to perform reasonably well the determination of the RIFLE categories when pre-morbid renal function was near normal and caution against the use of estimated bCr in patients with suspected CKD. This is clearly logical since the MDRD estimation method assumes that the patient has near-normal pre-morbid renal function, an assumption that obviously cannot be made in the case of suspected CKD,