mTOR inhibition in autosomal-dominant polycystic kidney disease (ADPKD): the question remains open

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Autosomal-dominant polycystic kidney disease (ADPKD) is the most common heritable kidney disorder with a prevalence of 1 in 400 to 1 in 1000 and accounting for ∼5% of the patient population requiring maintenance dialysis [1, 2]. Polycystins are required for the maintenance of differentiated epithelium, are expressed in kidney, liver and pancreas tubular cells, vascular smooth muscle cells and endothelium and play a role in multiple signalling pathways [3]. Disturbance of function results in increased tubular cell proliferation and apoptosis, fluid secretion resulting in progressive renal cyst formation and proliferation [1]. Mutations of the PKD1 gene, encoding polycystin-1, a membrane receptor, account for 85% of cases. A further 15% of cases are due to mutations of the PKD2 gene, encoding polycystin-2, a calcium-permeable channel binding polycystin-1. In general, *PKD1* disease is associated with a more severe clinical phenotype than *PKD2*, with earlier onset of end-stage kidney disease (mean age 54 years compared with 74 years) and greater numbers of renal cysts [1, 4, 5].

The mTOR pathway is regulated by polycystin and plays a role in multiple pathways, including the regulation of cell growth and proliferation. mTOR signalling is increased in murine models and human ADPKD, while mTOR inhibitors reverse disease progression in the former [6–8]. These findings together with the regression of hepatic disease seen in sirolimus-treated transplant recipients [9] have stimulated interest in mTOR inhibitors as a potential therapeutic agent for human ADPKD.

The challenge for triallists is the slow progression of clinical disease. Unlike the murine models of polycystic disease, human disease is characterized by progression over decades [1, 2]. The development of reliable surrogates for meaningful clinical outcomes has been a requirement for clinical research. In this context, the observational Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) has been a key influence [10]. Guidance published in 2006, it has provided a framework for subsequent clinical trials, establishing MRI-determined total kidney volume as a surrogate for disease progression. CRISP characterized a cohort of 232 adults with ADPKD from four US centres with a mean total kidney volume of 1060 mL at baseline and followed them for 3 years. The total kidney volume increased by an annual mean 204 ± 246 mL or $5.27 \pm 3.92\%$. Kidney function declined in those with a total kidney volume >1500 mL at baseline with estimated glomerular filtration rate (eGFR) falling by 4.33 ± 8.07 mL/min/year. Based on these findings, trials have been designed using the total kidney volume as a surrogate for disease progression, and have recruited participants with total kidney volumes of 1500 mL or more.

In 2010, two key randomized, placebo-controlled trials were published testing the hypothesis that mTOR inhibition would prevent or retard ADPKD disease progression. Walz *et al.* [11] examined the effect of treatment with 5 mg/day of the mTOR inhibitor, everolimus, for 2 years in 433 participants with ADPKD and CKD stage II or III. The mean eGFR at baseline was 55 mL/min and the total kidney volume was nearly 2000 mL. The study showed that despite retarding kidney size increase, mTOR inhibition with everolimus had no overall impact on kidney function. The total kidney volume increase was 301 mL over 2 years in the placebo group compared with 230 mL in the everolimus group ($P = 0.06$). However, there was no impact on eGFR, which declined by 8.9 mL/min in the everolimus group compared with 7.7 mL/min in the placebo group over 2 years. Proteinuria also increased in the everolimus group.

In the same issue, Serra *et al.* [12] reported the impact of sirolimus 2 mg daily compared with placebo over 18 months in 100 young adults with ADPKD, enlarging kidney size and near normal kidney function (eGFR 70 mL/min or higher). Sirolimus dosages were targeted to achieve levels of 4–10 µmol/L. Treatment had no impact on the total kidney volume or eGFR. Albuminuria increased in the sirolimus group but not the placebo group.

Together, the publication of these studies checked enthusiasm for pursuing studies of mTOR inhibitors in ADPKD. One explanation advanced for the results was that the degree of mTOR inhibition was inadequate [13, 14]. The regression of hepatic volume seen in sirolimus-treated kidney graft recipients with ADPKD [9] in the transplant setting occurred where sirolimus trough levels were typically 10–15 ng/mL. The dosing in ADPKD murine models is also substantially higher than

that used in humans. Furthermore, levels measured on peripheral blood samples may not correlate with those at the target tissue. An opportunistic assay of sirolimus levels in a transplanted ADPKD kidney showed measurable mTOR inhibition in peripheral blood but not in the renal tubular cells [15]. Other mechanisms for reduced exposure to the active drug are non-adherence, or as a result of dose reduction in response to adverse effects. Side effects limited the sirolimus levels in Serra *et al.* [12], although measured adherence to the prescribed dose was achieved. An alternative explanation advanced by Walz *et al.* [11] is that changes in volume do not perform as a surrogate for kidney outcomes in interventional trials of ADPKD. An observational cohort study currently in progress, more than 10 times the size of the CRISP study, has the potential to assess more accurately the relationship of total kidney volume and clinical outcomes (NCT01430494).

The question of adequate drug levels was the rationale for the SIRENA pilot study, a randomized crossover study of the impact of sirolimus over 6 months on the total kidney size in 21 adults with ADPKD [16]. The trial had an initial target sirolimus trough level of 10–15 ng/mL, reflecting levels used in transplantation, which was later revised down to 5–10 ng/mL. The study was complicated by a relatively high drop-out and adverse event rate. While it found no impact on the total kidney volume or GFR, there was a near-significant difference in cyst volume (<0.06) [16]. A further open-label pilot study examining the impact of mTOR inhibitor dose on ADPKD designed to randomize 30 participants to higher-dose sirolimus (target 5–8 ng/mL), lower dose (target 2–5 ng/mL) or standard care was due for completion in 2011(NCT00286156) [17].

In this setting, the open-label RAPYD study (EudraCT 2007-006557-25) randomized 55 participants with confirmed PKD1 ADPKD and an eGFR of 40–80 mL/min to one of three arms [18]. Participants received either higher- or lower-dose sirolimus (target troughs 6–8 and 2–4 ng/mL, respectively), or standard care for 24 months. All participants were treated with the angiotensin-converting enzyme (ACE) inhibitor ramipril. The study participants baseline had a mean total kidney of around 1700 mL, mild kidney function impairment (mean eGFR around 62 mL/min) and were not proteinuric (mean proteinuria around 0.12 g/day). The study did not find a statistically significant difference in total kidney volume growth between the three groups at the study end, cyst volume decreased significantly in both sirolimus groups while it increased in the comparator arm, with no clear difference between groups at the end of the study. The changes in eGFR over 24 months were also not different between the three groups, despite a significant decline in eGFR in the control group not seen in the other two groups. Safety signals were consistent with previous studies with proteinuria and hyperlipidaemia increasing in both sirolimus groups, significantly so in the higher-dose group. There were differences in reported (e.g. gender) and presumably unreported pertinent baseline characteristics which are to be expected, given the small sample size. The kidney volume measurements were not corrected for variables such as age and gender, shown to correlate with some kidney volume growth parameters in CRISP. These corrections were similarly not made in the larger mTOR inhibition trials but will potentially have a greater impact in this study in which, given its much smaller sample size, some imbalance of baseline characteristics is to be expected.

In the current study some will see tantalizing suggestions of benefit based on total kidney and on cyst volume, which may keep the mTOR inhibition hypothesis alive. The study certainly reinforces the safety signals of previous trials which will need to be accounted for in any evaluation of potential net benefit. At first glance, there is an apparent inconsistency in the results such as the finding of significant total kidney volume increase seen in the high dose and the control arm but not the low-dose sirolimus arm, or the lack of a difference in the rate of the volume or GFR changes between the three groups. Ultimately, these discrepancies are probably a function of the small sample size with none of the changes being statistically significant in a pilot that by its nature was underpowered to find a true difference for any reasonably expected effect size.

This study highlights the selection of appropriate outcomes as the fundamental ongoing issue for clinical trials in ADPKD: in a disease with noted phenotypic variability [19], is it appropriate or reasonable to use surrogates markers of progression (such as change in kidney size) as a marker of clinical benefit? The current study [18] observed rates of progression in kidney size and loss of kidney function that were substantially lower than had been expected based on the CRISP data. The mean increase in total kidney size in the comparator group was only 36 mL over 2 years, or around 1% per year compared with 5% in the CRISP cohort. Similarly, decline in eGFR was only 3.6 mL/min over 2 years, or around 3% per year, which is around half the rate expected from the CRISP study. Furthermore, these lower than expected rates of progression were despite the careful genotyping studies that ensure all participants had *PKD1* disease and not the more slowly progressive *PKD2*. A possible explanation for the discrepancy in CRISP and the later trials is that changes in background care may be impacting on disease progression. In the current study, all participants were treated with ACE inhibitors. However, renin–angiotensin inhibition alone is unlikely to be the full explanation for the lack of progression in the total kidney volume. Background rates of renin–angiotensin system inhibition were 80 and 42%, respectively, in the placebo-treated patients of two recent trials where the annual total kidney volume growth rates were 7.9 and 6.8%, respectively [11, 12]. The impact of renin–angiotensin inhibition and blood pressure control on disease progression is being tested in the HALT trials [20].

Of the 24 interventional trials for ADPKD currently listed with ClinicalTrials.gov, the median recruitment target is 85, making the majority of studies clearly underpowered for the detection of clinically important outcomes (Table 1). The two largest ongoing studies, TEMPO 3–4 and HALT-PKD A of 1445 and 548 respective participants with relatively preserved renal function, are powered on primary endpoints of kidney volume surrogates [20, 21]. The HALT-PKD B of 470 participants with eGFR of 25–60 mL/min is powered to assess the ability of

Table 1. Interventional trials for ADPKD currently registered with clinicaltrials.gov [21]

Intervention class	Trials	Combined target participant number		
	Number	Total	Median	Mean
mTOR inhibitors	8	795	57	99
Vasopressin receptor 2 antagonists	4	1696	113	424
Somatostatin analogues	4	496	79	124
Blood pressure-lowering treatment[a]	4	1328	315	332
Dietary salt intake	1	29	29	29
Nitrous oxide inhibition	1	75	75	75
Anti Src kinase inhibitor	1	190	190	190
Statin	1	100	100	100
Traditional Chinese Medicine	1	150	150	150
Total		4859	90	194

[a]Blood pressure-lowering treatment including agents acting on the renin–angiotensin system.

angiotensin receptor blockade (ARB) to achieve a 25% reduction in the rate of change of eGFR beyond background ACE inhibitor treatment and tight blood pressure control over 4–6 years [20]. The figure of 25% reduction is based on clinical importance and would be on a par with that achieved by ARB compared with placebo or calcium channel blocker in the larger IDNT study [22]. These large studies will yield important insights into the clinical progression of ADPKD and at the very least provide firm evidence on the occurrence of hard clinical outcomes and the progression of eGFR decline.

There is a clear need to power future trials for clinically important outcomes, such as differences in kidney function or rates of kidney failure, and to do so conservatively so that trials have a reasonable likelihood of demonstrating important benefits where these exist. Appropriately powered trials will also provide clearer and more reliable data regarding the safety of these agents, allowing fully informed therapeutic decisions to be made.

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