

mTOR Inhibitors in Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is a common cause of inherited renal failure¹ that is characterized by the progressive formation of renal cysts, which leads to end-stage renal disease in mid-adulthood. Furthermore, massive renal enlargement has a number of untoward consequences, including chronic pain, hypertension, and cyst infections. Approximately 85% of ADPKD cases are caused by mutations in the *PKD1* gene that encodes a large membrane receptor. The remaining 15% of cases result from mutations in the *PKD2* gene, a calcium-permeable channel that binds to PKD1. The accelerated pace of scientific discovery in the field has led to an intensive search for therapeutic targets that might slow cyst growth and thereby delay the onset of renal failure.

Clinical trials testing the efficacy of inhibitors of the mammalian target of rapamycin (mTOR) in patients with ADPKD have been much anticipated, given the compelling preclinical data implicating aberrant mTOR signaling in the pathogenesis of ADPKD.² This serine–threonine kinase coordinates cell growth and proliferation, processes that are dysregulated in patients with polycystic kidney disease. Increased mTOR signaling has been detected in a subgroup of cysts from both mice and humans with ADPKD.^{3,4} In addition, an mTOR inhibitor, sirolimus, was effective in ameliorating cyst growth and preserving renal function in mice with early conditional inactivation of *Pkd1*.⁵

The prospect of therapeutic agents has served to focus attention on the challenges inherent in executing definitive clinical trials involving patients with ADPKD, since the natural history of the disease is characterized by gradual cyst growth over decades, coupled with a gradual decline in renal function. Thus, trials relying on traditional end points such as serum creatinine level are impractical, since years of follow-up would be required to detect any benefit. On the basis of this conceptual view of the progression of polycystic kidney disease, the CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease) study was initiated to determine whether renal enlargement could serve as a surrogate for early disease progression.⁶ The CRISP study showed that total kidney and cyst

volumes increase exponentially (approximately 5% annually) and that magnetic resonance imaging (MRI) reproducibly detected this change. In the subgroup of patients whose total kidney volume exceeded 1500 ml, renal growth correlated with a decline in glomerular filtration rate (GFR). It is assumed that effective therapies should slow or stall renal enlargement and, by extrapolation, preserve renal function.

The publication of the CRISP study set the stage for the two clinical trials reported in this issue of the *Journal*, which suggest that the use of mTOR inhibitors in patients with ADPKD may be more complicated than expected. In the larger of the two studies, Walz et al.⁷ describe the results of a 2-year, placebo-controlled trial of another mTOR inhibitor, everolimus (ClinicalTrials.gov number, NCT00414440) involving 433 patients with ADPKD with stage II or III chronic kidney disease and an average baseline renal volume greater than 1500 ml. Surprisingly, although everolimus appeared to slow the increase in total kidney volume, this change did not correlate with improvement in the estimated GFR. In fact, after a transient improvement, the estimated GFR declined more rapidly in the everolimus group than in the placebo group, leading the authors to conclude that smaller may not necessarily mean better.

In a complementary study, Serra et al.⁸ compared sirolimus with placebo in 100 patients between the ages of 18 and 40 years who had early-stage ADPKD (GFR, ≥ 70 ml per minute per 1.73 m² of body-surface area) and an average total kidney volume of approximately 1000 ml (ClinicalTrials.gov number, NCT00346918). In contrast to the study by Walz et al., Serra et al. found that treatment with sirolimus for 18 months did not slow kidney growth, as measured on MRI. Because this study was conducted in patients with early-stage disease, there was no difference in GFR between the two groups. Taken together, these studies suggest that therapy with these mTOR inhibitors will not be the sought-after magic bullet, regardless of ADPKD stage.

So why are these results discordant with those of preclinical studies? In patients with later-stage ADPKD, such as those studied by Walz et al., the disease may have been too advanced to yield

functional benefit, despite a reduction in renal size. In fact, processes such as renal fibrosis, which may drive GFR decline in late stages of ADPKD, are likely to be independent of changes in renal volume. In addition, inhibition of the mTOR pathway could compromise the normal compensatory hypertrophy that preserves GFR in patients with chronic kidney disease. Since glomerular hyperfiltration is considered detrimental over time, interfering with this process through long-term mTOR inhibition might conceivably provide long-term benefits not realized in this 2-year trial.

In contrast to results with everolimus, Serra et al. report that sirolimus at a target dose of 2 mg per day was ineffective in slowing renal growth. This finding raises the possibility that the standard dose of sirolimus is inadequate to achieve mTOR inhibition in renal cysts. In support of this theory, Canaud et al.⁹ assayed mTOR inhibition in a renal-transplant recipient who had inadvertently received an ADPKD kidney and was treated with sirolimus. Sirolimus therapy reduced mTOR activity in peripheral-blood mononuclear cells but not in renal tubular cells. In addition, the doses of sirolimus that were used to treat *Pkd1* mutant mice were far in excess of what can be used safely in humans. Drugs that can achieve better renal inhibition of mTOR activity with an acceptable safety profile might yet be useful.

The challenge of achieving adequate mTOR suppression without dose-limiting toxic effects highlights an important concern. In the study by Walz et al., approximately one third of patients did not complete the study protocol, many because of drug-related adverse events. The drop-out rate was significantly lower in the study by Serra et al., but the sirolimus dose was approximately 25% lower than intended because of dose-limiting side effects. In addition, some of the adverse events, such as chronic proteinuria and hyperlipidemia, could have serious long-term consequences. This is especially worrisome in patients with ADPKD, which is a chronic disease that is often indolent and variable in its course.

There is one important implication of the everolimus study that deserves further comment. It has been assumed that renal-volume growth would be a suitable surrogate marker for therapeutic efficacy. Yet in the study by Walz et al., everolimus was able to slow kidney growth in

the absence of a stabilizing effect on renal function. This finding is similar to results reported by Hogan et al.,¹⁰ who used a long-acting somatostatin analogue to treat a small number of patients with ADPKD (ClinicalTrials.gov number, NCT00426153). Although it seems intuitively clear that there must be some link between cyst burden and functional impairment, the relationship is not straightforward, as illustrated by the incredible diversity of renal volumes associated with any given estimated GFR. This raises the concern that one might be able to reduce cyst growth without having an effect on renal function. The study by Walz et al. strongly suggests that the two outcomes can be unlinked.

So where do we go from here? In the short term, these results may affect the design of future intervention studies as we reassess the value of using renal-volume measurements as a primary end point. Longer study timelines also may be required to show true functional efficacy. The discrepancy between preclinical data and the results of these trials in humans underscores the need for better preclinical models to predict human outcomes. The *Pkd1* mouse model treated with sirolimus had a rapid-onset form of the disease that differs from the usual pattern of disease in humans. We have found that progression of polycystic kidney disease in mice varies according to the timing of *Pkd1* inactivation.¹¹ A murine model with a slower, later onset might provide a closer approximation of the human clinical condition. Finally, there is little question that we need better tools for assessing the effects of our interventions on renal function in humans. This is a problem common to almost all other forms of chronic kidney disease and one that urgently needs a solution.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Treating Underinsurance

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Whereas recent attention to health care reform has focused on insuring uninsured Americans, the report in this issue of the *Journal* by Kogan et al. addresses a different and important problem — “underinsurance.” Using a broad definition, Kogan et al. find that large numbers of U.S. children and adolescents have full-year insurance coverage but still face problems getting needed care.¹ In fact, applying their definition, they found more children who were underinsured (almost 20% of U.S. children) than children who were uninsured, either year-round or intermittently (15.1%). Furthermore, the problems faced by underinsured children in terms of health care quality and access were more similar to those of uninsured children than to those of children with good, year-round insurance.

The authors’ definition of “underinsurance” is not new; they previously reported that almost one third of all children with special health care needs were underinsured.² The definition in these studies uses any of three main indicators of underinsurance: lack of needed benefits or services, limited access to providers, or out-of-pocket costs that parents considered unreasonable. Of these, the most common basis for determining “underinsurance” was a parental report that coverage of costs was not reasonable. Other studies may use specific levels of out-of-pocket costs (for example, an earlier study using a more conservative definition reported underinsurance in 13.8% of children with special health care needs).³ The data available to Kogan et al. do not allow comparison of parents’ perceptions of reasonableness with measures of ac-

tual out-of-pocket costs. If the criterion in this study for “reasonableness of costs” had been excluded, only 8 to 9% of children would be considered underinsured.

Despite this limitation, the findings of Kogan et al. can help frame key issues at this critical juncture in health care reform. An important finding is that children with chronic health conditions have a higher risk of underinsurance than other children. In an earlier study,² these authors reported a lower rate of underinsurance among children with special health care needs who had public insurance than among those who had private insurance, probably reflecting better coverage of long-term benefits such as specialized therapies in Medicaid, with little or no co-payment required. Although the current study does not compare the benefits of public insurance as opposed to private insurance among children, families with incomes between 200% and 399% of the federal poverty line had the highest rates of underinsurance; if publicly insured, this group was likely to have been covered by the State Children’s Health Insurance Program (SCHIP). (SCHIP was created in 1997 and reauthorized as the Children’s Health Insurance Program [CHIP] in February 2009.) Children with chronic conditions (like adults with chronic conditions) have many more encounters with the health system than do healthy children; consequently, there are more opportunities for them to have the experience of unmet needs. Their much higher health care utilization can also generate high unreimbursed costs.⁴ The higher rates of underinsurance among children with spe-