

## Randomized Intervention Studies in Human Polycystic Kidney and Liver Disease

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Autosomal dominant polycystic disease (ADPKD) is the most common life-threatening genetic disease in the United States. ADPKD is more common than Huntington disease, hemophilia, cystic fibrosis, sickle cell disease, Down syndrome, and myotonic dystrophy *combined*.<sup>1</sup> The increase in kidney cyst volume over time correlates with hypertension and progressive renal dysfunction, yet, to date, there is no established intervention to slow or prevent the renal cyst growth. Increased proliferation accompanies renal cyst growth, and recent research in non-orthologous experimental animals and patients with ADPKD suggests aberrant activation of the Ser/Thr kinase mammalian target of rapamycin (mTOR), which modulates cell growth and proliferation.<sup>2–5</sup> Recently, rapamycin was shown to have dramatic effects on liver cyst volumes in humans<sup>6</sup> and in an orthologous rodent model with conditional inactivation of the PKD1 gene.<sup>7</sup> The results demonstrate that mTOR inhibition with rapamycin decreases cyst growth, fibrosis, and proliferation and improves renal function. Of interest, there was regression of cyst burden, which may have been due to increased apoptosis among the cystic epithelium.

Perico *et al.*<sup>8</sup> in this issue of *JASN* performed a renal safety and efficacy study to examine further this potential pathogenetic ADPKD pathway in humans. This randomized crossover study examined the effect of sirolimus (rapamycin) over 6 months on progression of ADPKD compared with conventional therapy. The main efficacy variable was the effect on total kidney volume, but renal cyst and parenchymal volumes were also measured. The effect of sirolimus on GFR was also examined relative to kidney volume and structure changes. The kidney volumes

were measured by spiral computerized tomography and GFR by the iohexol plasma clearance techniques. There were no differences in the increase in total renal volume or change in GFR between sirolimus and conventional treatment; however, the absolute cyst volume was virtually stable in the sirolimus arm, whereas it increased with conventional treatment (mean 4.5 *versus* 54.9 ml;  $P < 0.06$ ). When relative cyst volume changes were compared, the increase in cyst volume with sirolimus was significantly less than with conventional therapy ( $P = 0.02$ ). The most impressive change was that parenchymal volume actually increased significantly with sirolimus and was stable with conventional therapy (mean 26.0 *versus*  $-2.7$  ml;  $P < 0.009$ ). One potential explanation for this latter finding, suggested by the authors, was that less cystic compression of renal parenchyma and vasculature with sirolimus treatment led to increased parenchymal volume.

There are several caveats regarding this 6-month study. There was a 28% dropout rate (six of 21), and the statistical analysis was not by intention-to-treat. Ten of the remaining 15 patients developed aphthous stomatitis. In this 6-month study, sirolimus treatment was associated with statistically significant increases in liver enzymes (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) and lipids (total cholesterol, LDL cholesterol, and triglycerides), a decrease in hematocrit, and an increase in urinary albumin/protein excretion, none of which was observed with conventional therapy. This is potentially bothersome regarding possible lifelong therapy for ADPKD. Thus, results of larger and longer follow-up studies of mTOR inhibitors in patients with ADPKD will be very important.

In this issue of *JASN*, another interventional study examined the effects of a somatostatin analogue in patients with polycystic liver and kidney diseases.<sup>9</sup> There is considerable evidence for a role of cAMP in epithelial proliferation and fluid secretion in experimental renal and hepatic cystic disease. In that regard, somatostatin blunts hepatic cyst expansion by blocking secretin-induced cAMP generation and fluid secretion by cholangiocytes.<sup>10</sup> Hogan *et al.*<sup>9</sup> performed a 1-year randomized, blinded study to examine whether octreotide, a long-acting somatostatin, would decrease liver volume compared with placebo in 42 patients with severe polycystic liver disease (34 with ADPKD and eight with autosomal dominant polycystic liver disease). By magnetic resonance imaging, the mean liver volume decreased from 5907 to 5557 ml ( $4.95 \pm 7.00\%$ ) in the octreotide group ( $n = 28$ ) compared with 5374 to 5361 ml ( $0.92 \pm 7.00\%$ ) in the placebo group ( $n = 14$ ). This difference (mean 4.95 *versus* 0.92%) was significant ( $P = 0.045$ ). The self-reported SF-36 form demonstrated a sig-

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nificant improvement in perception of body pain and physical activity in octreotide-treated patients. The blinding may be difficult in this self-reported analysis, because a large number of the octreotide-treated patients had gastrointestinal adverse effects such as diarrhea. Nevertheless, the decreased perception of pain with octreotide is potentially an important finding, because abdominal and back pain can be a major complaint in patients with large polycystic livers. A decrease in liver size with octreotide could potentially preclude surgical intervention.

Secondary end points in this study were the effects of octreotide on kidney volume and GFR. The mean kidney volume was stable before and after octreotide (1143 to 1129 ml [ $0.25 \pm 7.50\%$ ]) compared with an increase in mean kidney volume in the placebo group (803.0 to 873.5 ml [ $8.6 \pm 10.0\%$ ]). The  $P$  value for the  $\Delta\%$  change was significantly different between the octreotide and placebo groups (mean  $0.25$  versus  $8.60\%$ ;  $P = 0.045$ ).

This human study by Hogan *et al.*<sup>9</sup> translates the experimental findings in polycystic PCK rats that demonstrate intraperitoneal octreotide for 4 to 16 weeks decreases liver and kidney size as well as cystic and fibrotic scores.<sup>10</sup> This 12-month randomized study<sup>9</sup> supports a previous randomized 6-month study in which a somatostatin analogue decreased kidney volume compared with placebo.<sup>11</sup> The results of that study demonstrated an effect on kidney volume of a long-acting somatostatin inhibitor in 12 patients with ADPKD. These patients had a mean total kidney volume of 2435 ml and a mean serum creatinine of 1.9 mg/dl. Compared with placebo, the patients with ADPKD in the somatostatin analogue arm exhibited a significant decrease in kidney volume as compared with placebo ( $2.2 \pm 3.7$  versus  $5.9 \pm 5.4$ ;  $P < 0.01$ ). These results suggest that intervention may be beneficial even in advanced ADPKD. In neither of these small, short-term studies was there a significant difference in GFR when the somatostatin analogue was compared with placebo.<sup>8,9</sup>

Another approach to decrease cAMP and renal cyst growth was demonstrated in several experimental models of PKD with administration of V2 receptor antagonists.<sup>12–14</sup> Arginine vasopressin activates V2 receptors in the principal cells along the collecting duct by stimulating cAMP, an effect that can be blocked with V2 receptor antagonists. Of interest, somatostatin also inhibits the effect of arginine vasopressin to stimulate cAMP.<sup>15</sup> There is now a large ongoing randomized trial (Tolvaptan Efficacy and Safety in Management of Polycystic Kidney Disease and Its Outcomes [TEMPO]) examining the effect of an orally active V2 receptor antagonist, tolvaptan, to decrease kidney volume in patients with ADPKD.<sup>16</sup>

Thus, the results of two small, single-center studies published in this issue of *JASN* give hope that increases in polycystic liver and kidney volume can be attenuated and thereby improve morbidity and mortality in patients with ADPKD.<sup>8,9</sup> Multicenter studies with adequate statistical

power and follow-up duration are needed to test this possibility further. In the ADPKD kidney studies, in addition to observing an effect on the total volume and cyst and parenchymal volumes of the kidney, an intervention that demonstrates protection against the loss of GFR would be important. Last, because of the embryonic formation of cysts, early intervention in children with ADPKD may be necessary to demonstrate optimal efficacy.<sup>17</sup>

## DISCLOSURES

R.W.S. is a consultant for Otsuka Pharmaceuticals.

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See related articles, “Sirolimus Therapy to Halt the Progression of Autosomal Dominant Polycystic Kidney Disease: The Sirena Study,” on pages 000–000, and “Randomized Clinical Trial of Long-Acting Somatostatin for Autosomal Dominant Polycystic Kidney and Liver Disease,” on pages 000–000.