Randomized Clinical Trial of Long-Acting Somatostatin for Autosomal Dominant Polycystic Kidney and Liver Disease

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ABSTRACT

There are no proven, effective therapies for polycystic kidney disease (PKD) or polycystic liver disease (PLD). We enrolled 42 patients with severe PLD resulting from autosomal dominant PKD (ADPKD) or autosomal dominant PLD (ADPLD) in a randomized, double-blind, placebo-controlled trial of octreotide, a long-acting somatostatin analogue. We randomly assigned 42 patients in a 2:1 ratio to octreotide LAR depot (up to 40 mg every 28 ± 5 days) or placebo for 1 year. The primary end point was percent change in liver volume from baseline to 1 year, measured by MRI. Secondary end points were changes in total kidney volume, GFR, quality of life, safety, vital signs, and clinical laboratory tests. Thirty-four patients had ADPKD, and eight had ADPLD. Liver volume decreased by 4.95% ± 6.77% in the octreotide group but remained practically unchanged (+0.92% ± 8.33%) in the placebo group ($P = 0.048$). Among patients with ADPKD, total kidney volume remained practically unchanged (+0.25% ± 7.53%) in the octreotide group but increased by 8.61% ± 10.07% in the placebo group ($P = 0.045$). Changes in GFR were similar in both groups. Octreotide was well tolerated; treated individuals reported an improved perception of bodily pain and physical activity. In summary, octreotide slowed the progressive increase in liver volume and total kidney volume, improved health perception among patients with PLD, and had an acceptable side effect profile.

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Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the development of renal cysts and a variety of extrarenal manifestations of which polycystic liver disease (PLD) is the most common.[1] It is caused by mutations in one of two genes: *PKD1* or *PKD2*. *PKD1* mutations are responsible for approximately 85% of clinically detected cases. Autosomal dominant PLD (ADPLD) also exists as a genetically distinct disease with few or absent renal cysts. Like ADPKD, ADPLD is genetically heterogeneous, with the first two genes identified (*PRKCSH* and *SEC63*) accounting for approximately one-third to one-half of isolated ADPLD cases.[2–5]

Chronic symptoms are frequently associated with massively enlarged PLD, including abdominal distension and pain, dyspnea, gastroesophageal reflux, and early satiety, which may lead to malnutrition, mechanical lower back pain, inferior vena cava, hepatic and portal vein compression (leading to hypotension

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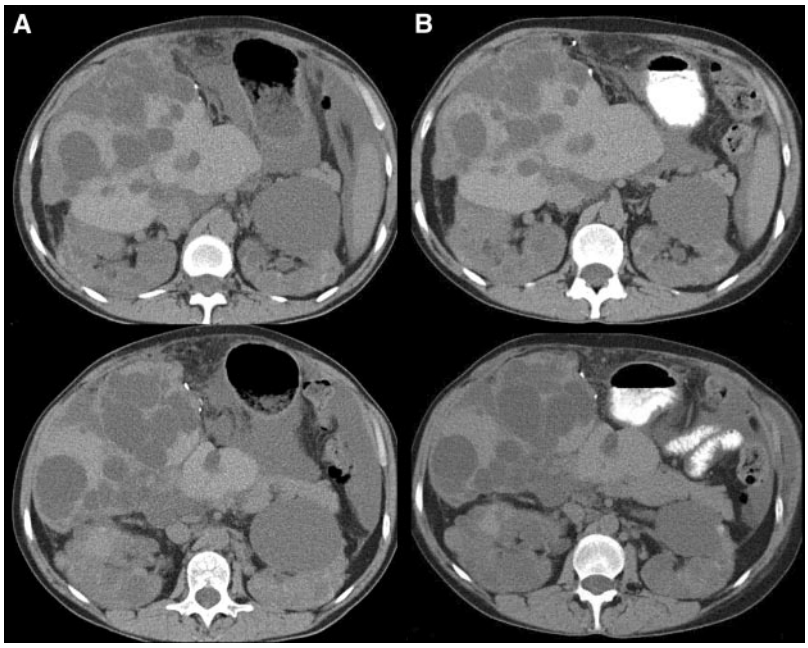

Figure 1. Administration of octreotide LAR to a patient with severe PLD resulted in decreased liver and kidney volumes. CT axial sections immediately before (A) and after 8 months of treatment with octreotide (B) are shown. Total liver volume decreased by 18% from baseline, and total kidney volume decreased by 12%.

and inferior vena cava thrombosis, hepatic venous outflow obstruction, and portal hypertension), and biliary obstruction. Surgical approaches may be associated with definitive palliation but are also associated with a risk of morbidity and mortality.[6]

Liver cysts arise by excessive proliferation of cholangiocytes and dilation of biliary ductules and peribiliary glands. Alterations in intracellular calcium homeostasis and 3′-5′-cAMP stimulate mitogen-activated protein kinase-mediated cell proliferation and cystic fibrosis transmembrane conductance regulator-driven chloride and fluid secretion.[7] Cyst growth is enhanced by growth factors and cytokines secreted into the cyst fluid.[8] Downstream activation of mTOR likely contributes to cystogenesis.[9] Somatostatin may blunt cyst development by acting at multiple levels: inhibition of secretin release by the pancreas[10]; inhibition of secretin-induced cAMP generation and fluid secretion in cholangiocytes[11–13]; vasopressin-induced cAMP generation and water permeability in collecting ducts[14–17] by its effects on Gi protein-coupled receptors; and suppression of the expression of IGF-1, vascular endothelial growth factor, and other cystogenic growth factors and of downstream signaling from their receptors.[14–18]

To determine whether octreotide could be effective in the treatment of PLD, we examined the effects of octreotide in the PCK rat, a recessive model of polycystic liver and kidney disease. We found that octreotide significantly reduced cAMP levels and hepatic cystogenesis *in vitro* and *in vivo*.[19] In patients who underwent liver resections for massive PLD, we had observed that administration of octreotide reduced the rate of fluid secretion from unroofed cysts. In one patient with persistent ascites, intramuscular administration of octreotide LAR 40 mg monthly for 8 months was accompanied by a 17.8% reduction in liver volume from 2833 ml to 2330 ml (Figure 1). Two similar instances have been recently reported by van Keimpema *et al.*[20] Finally, a pilot study showed that administration of octreotide LAR significantly inhibited kidney and cyst enlargement in patients with ADPKD.[21] Encouraged by the results of the preclinical studies, anecdotal clinical experiences, and the pilot study in ADPKD, we initiated a pilot randomized, placebo-controlled, double-blind clinical trial of octreotide LAR in severe PLD.

RESULTS

A study flow diagram summarizing participant screening, enrollment, randomization, and disposition is shown in Figure 2.

Baseline Characteristics

Baseline patient characteristics were similar between the two groups (Table 1). Of the 42 patients who underwent randomization, 28 were assigned to receive octreotide and 14 to receive placebo. Five enrolled patients had a history of liver cyst aspiration/sclerosis, seven of liver fenestration (four octreotide, three placebo), and four of liver resection (one assigned octreotide and three to placebo). At least five had been offered a liver transplant. Four patients (three in the octreotide and one in the placebo group) had undergone renal transplantation before enrollment, and one patient (in the placebo group) had bilateral nephrectomies before transplantation. Three were receiving cyclosporine with azathioprine/mycophenolate mofetil, and one was receiving prednisone and mycophenolate mofetil. No patients were on sirolimus. For the analysis of kidney data, 13 patients were excluded because of a diagnosis of ADPLD (eight patients: four to octreotide, four to placebo), renal transplantation (four patients), and missing kidney data due to incomplete image coverage (one patient, assigned to placebo). Baseline liver volumes ranged from 2234 to 11766 ml in the octreotide group ($n = 28$) and from 2239 to 13,148 ml in the placebo group ($n = 14$). Baseline total kidney

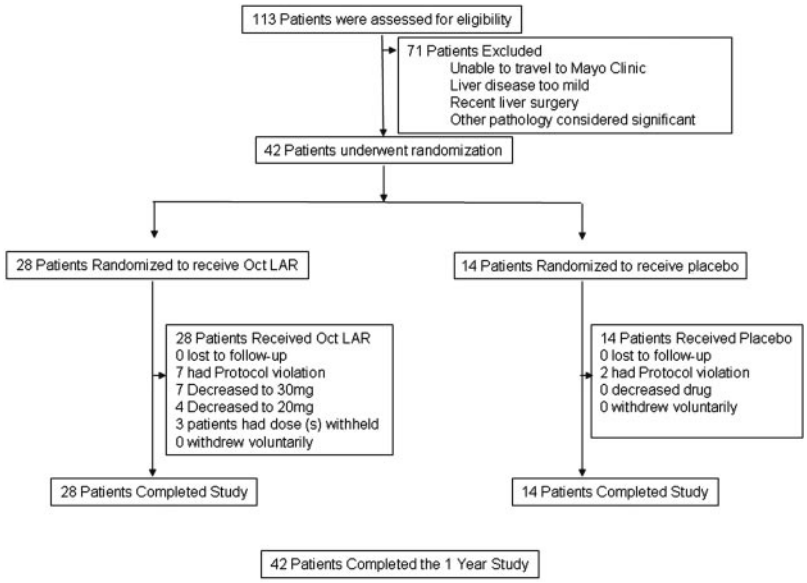

Figure 2. Study flow diagram. Protocol violations were as follows: In the octreotide (Oct) arm, five injections of masked study drug and two study visits occurred outside of the protocol window. One 24-hour urine collection was obtained after the study visit. In the placebo arm, two injections of masked study drug and one study visit occurred outside of the protocol window.

Table 1. Baseline clinical data according to study group

	Octreotide (n = 28)	Placebo (n = 14)	P
Male, *n* (%)	5 (17.9)	1 (7.1)	
Female, *n* (%)	23 (82.1)	13 (92.9)	0.64
Mean age, yr	49.7 ± 9 (34.8 to 69.3)	50.3 ± 7.3 (38.8 to 65.7)	0.56
Weight, kg	76.0 ± 20.2 (50.3 to 129.5)	70.9 ± 10.9 (55.6 to 92.8)	0.66
BMI, kg/m^2	26.3 ± 5.77 (18.3 to 41.3)	24.4 ± 2.98 (220.7 to 29.9)	0.46
Serum creatinine, mg/dl	1.1 ± 0.4 (0.6 to 2.6)	1.1 ± 0.5 (0.7 to 2.3)	0.53
GFR[a], ml/min per 1.73 m^2	70 ± 27 (20 to 124)	71 ± 27 (22 to 115)	0.85
Fasting plasma glucose, mg/dl	93.4 ± 11.2 (80 to 132)	93.6 ± 7.8 (88 to 110)	0.66
Urine albumin, mg/24 h	65 ± 123 (3.0 to 470)	130 ± 237 (3 to 797)	0.57
SBP, mmHg	122.1 ± 13.2 (103 to 159)	120.5 ± 13.5 (90 to 137)	0.83
DBP, mmHg	79.8 ± 8.9 (59 to 102)	79.1 ± (54 to 90)	0.86
ADPKD			0.40
PKD1	16	9	
PKD2	5	1	
NMD	3	0	
ADPLD			0.74
PRKCSH	3	1	
SEC63	0	1	
NMD	1	2	
Liver volume, ml	5907.7 ± 2915.0 (2234.1 to 11,766.1)	5373.9 ± 3565.4 (2238.6 to 13,148.1)	0.40
Total kidney volume, ml[a]	1142.9 ± 826.9 (320.3 to 3351.5)	803.0 ± 269.1 (443.4 to 1210.7)	0.86

Unless indicated otherwise, data are mean ± SD (range).
[a]Kidney volume/GFR: four transplant patients, eight ADPLD patients, and one patient with missing values were removed from this analysis. BMI, body mass index; NMD, no mutation detected.

volumes ranged from 320 ml to 3352 ml in the octreotide group (n = 21) and from 443 to 1211 ml in the placebo group (n = 8).

Patient Genotypes

Thirty-four patients had ADPKD; of these, 25 had a *PKD1* mutation and six a *PKD2* mutation; in three patients no mutation was detected. Eight patients had ADPLD; of these, four had a *PRKCSH* mutation and one a *SEC63* mutation; in three patients no mutation was detected. ADPKD and ADPLD genotypes and phenotypes were equally distributed between the octreotide and placebo groups (Table 1).

Main Outcomes

Liver Volumes.

Liver volumes in the octreotide group were 5908 ± 2915 ml and 5557 ± 2659 ml at baseline and 12 months, respectively (Figure 3A). Liver volumes in the placebo group were 5374 ± 3565 ml and 5361 ± 3331 ml at the baseline and 12-month visits, respectively. Twenty-one of the 28 octreotide-treated patients experienced a reduction in liver volume during the 12 months of treatment; this was not affected by the underlying genotype (Figure 3B). On average, liver volume decreased by 4.95% ± 6.77% in the octreotide group compared with a small increase (0.92% ± 8.33%) in the

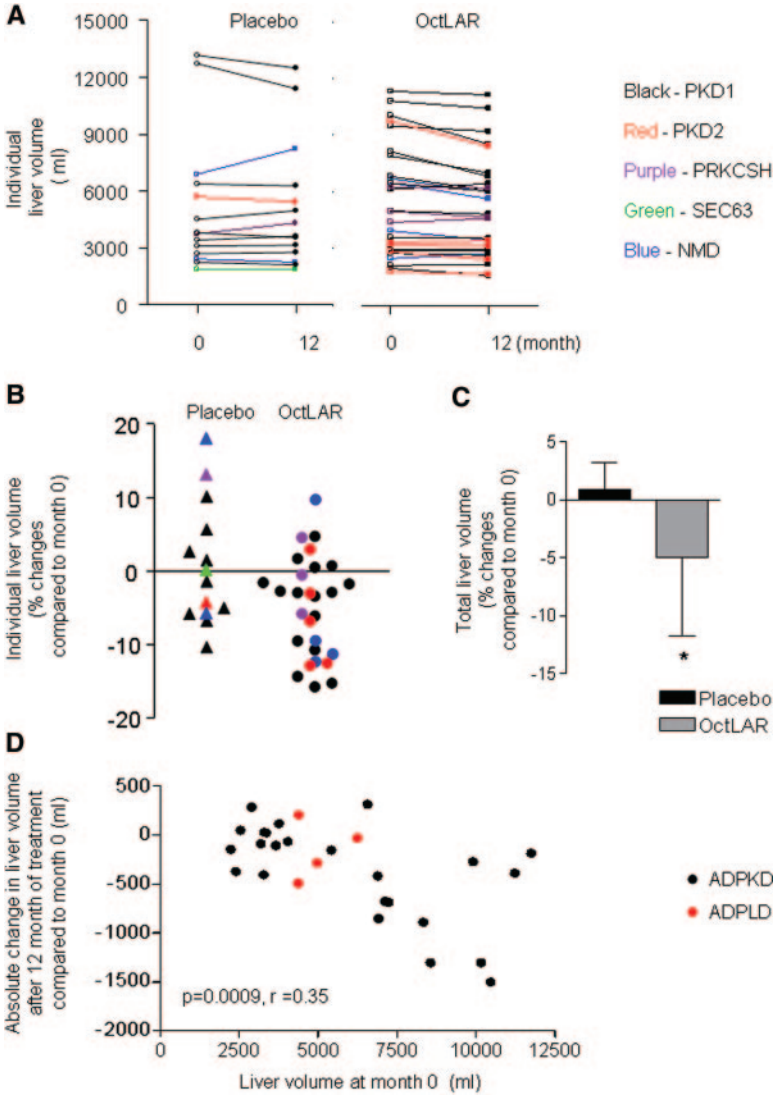

Figure 3. Octreotide therapy (Oct-LAR) decreased total liver volumes. (A) Total liver volumes in each individual patient in placebo (left) and octreotide (right) groups before (0 months) and after (12 months) treatment. (B) Changes in liver volumes in each patient expressed as a percent of change after 12 months of treatment compared with month 0 in placebo and octreotide groups. (C) Averaged changes in total liver volume (mean ± SD) in placebo and octreotide-treated groups; *$P = 0.048$. (D) Correlation between liver volumes (measured at 0 months) and response to absolute changes in total liver volumes after 12 months of treatment. Individuals with larger liver volumes had greater response to treatment. Colored symbols and lines represent individual patient genotypes (A and B) or by disease group in D. NMD, no mutation detected.

placebo group ($P = 0.048$, rank-sum test; Figure 3C). Changes in liver volume in response to octreotide treatment were significantly correlated with baseline liver volumes—patients with larger livers had larger reductions (Figure 3D).

Kidney Volumes.

Thirteen patients were excluded from the kidney analysis (see Baseline Characteristics for details). Total kidney volumes in the octreotide group were 1143 ± 827 and 1129 ± 796 ml at the baseline and 12-month visits, respectively (Figure 4A). Total kidney volumes in the placebo group were 803 ± 269 ml and 874 ± 306 ml at the baseline and 12-month visits, respectively (Figure 4A). Five of eight patients in the placebo group experienced an increase in total kidney volume during the 12 months of treatment (Figure 4B). In the placebo group, total kidney volumes increased by 8.61% ± 10.07% compared with 0.25% ± 7.53% in the octreotide group ($P = 0.045$, rank-sum test; Figure 4C). Changes in kidney volume in response to octreotide treatment were significantly correlated with baseline kidney volumes—patients with larger kidneys had larger reductions (Figure 4D).

Secondary Outcomes

Kidney Function.

GFR measured by iothalamate clearance in 30 ADPKD patients decreased from 68.1 to 64.6 ml/min per 1.73 m^2 (−5.1%) in the octreotide group ($n = 21$) compared with a decrease from 70.1 to 65.7 ml/min per 1.73 m^2 (−7.2%) in the placebo group ($n = 9$; $P = 0.98$; Table 2). There was no significant difference in the rates of change in serum creatinine between the octreotide (+3.5%) and the placebo (+5.6%) groups ($P = 0.56$; Table 2).

Quality of Life.

Two subdomains in the health-related quality of life (HRQoL) questionnaire (SF-36; Table 3)—that is, physical role, which assesses physical activity (60 to 74, $P = 0.04$) and bodily pain (68 to 76, $P < 0.02$—significantly improved in the octreotide-treated group. No significant changes were seen in the placebo-treated group. No other HRQoL subdomains changed significantly over the course of the study.

Tolerability

Eighteen patients had symptoms after the test dose; 11 had mild diarrhea, five had abdominal cramps, six developed nausea, two complained of gas, and one each had vomiting, dizziness, and headache. One patient with moderate diarrhea after the test dose was initiated on a reduced dose (20 mg).

The target dose was reached in 41 (97%) of 42 patients. Seven octreotide doses were withheld in three patients (Figure 5). The dose was reduced to 30 mg in seven and 20 mg in four patients receiving octreotide, mostly because of diarrhea/loose stools, especially in the first 2 weeks after an injection (Figure 5). The commonest reported side effect was injection site pain: 21 (75%) of 28 compared with 3 (21%)

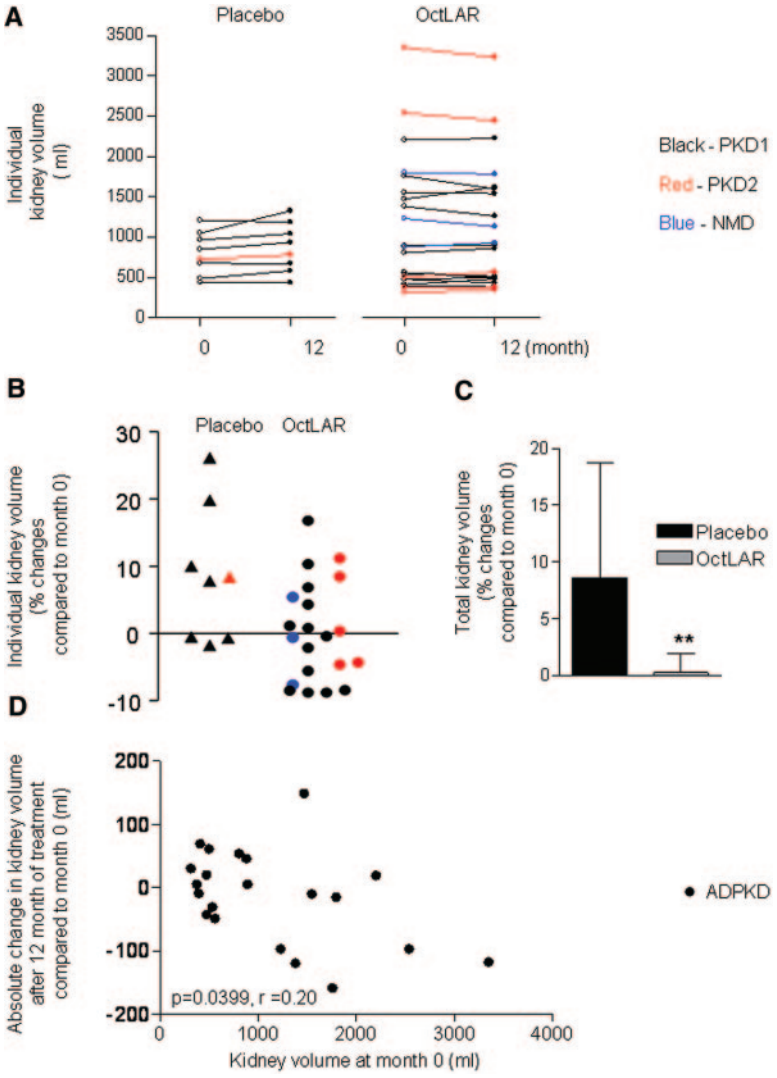

Figure 4. Octreotide therapy (OctLAR) stalled kidney growth in treated individuals. (A) Total kidney volumes in each individual patient in placebo (left) and octreotide (right) groups at baseline (0 months) and after (12 months) treatment. (B) Changes in kidney volumes in each patient expressed as a percent change after 12 months of treatment compared with month 0 in placebo and octreotide groups. (C) Averaged changes in total kidney volume (mean ± SD) in placebo and octreotide-treated groups; $^{**}P = 0.045$. (D) Correlation between kidney volumes (measured at 0 months) and response to absolute changes in total kidney volumes after 12 months of treatment. Individuals with larger kidney volumes had greater response to treatment. Colored symbols and lines represent individual patient genotypes (A and B); NMD, no mutation detected.

of 14 on placebo. Injection site granulomas were reported in 5 of 28 patients receiving octreotide, with no occurrence in the placebo group.

Diarrhea grade 1 (an increase of less than four stools per day over baseline) was reported in 17 (61%) of 28, and abdominal cramping, bloating, and gas in 14 (50%) of 28 patients in the octreotide arm compared with 4 (28%) of 14 and 3 (21%) of 14, respectively, in the placebo arm. One patient on octreotide developed steatorrhea and weight loss. Despite withholding four doses and later recommencement of 20 mg while on pancreatic supplements, his symptoms persisted. Because he completed the 12 months in the study, his data were included in the analysis.

Asymptomatic nonobstructing cholelithiasis was identified in one patient, and another had gallbladder sludge. Both findings were present before assignment to octreotide and remained clinically stable on therapy.

One patient developed moderate alopecia after three full doses. Octreotide was held for 2 months for hair regrowth and then restarted 20 mg for 1 month and increased to 30 mg until completion with minimal hair loss.

One patient receiving octreotide developed symptomatic bradycardia requiring an emergency room visit after her sixth 40-mg dose. One dose was held, and then the participant was recommenced on 20 mg for 5 months and then increased to 30 mg. No patient receiving placebo required a dose reduction.

Safety

Over the 1-year study period, three patients receiving octreotide were hospitalized for causes deemed to be unrelated to the study intervention (bacteremia associated with nephrolithiasis and a urinary infection, abdominal pain and fever responding to antibiotic treatment, and incarcerated abdominal hernia). No serious adverse events occurred in the first year in the patients receiving placebo.

Plasma glucose levels increased 10% from baseline compared with a 2% increase in placebo ($P = 0.02$) after commencing octreotide treatment, but no patient developed diabetes (Table 2). No significant fluctuations in cyclosporin levels were observed in the three renal transplant recipients receiving both medications.

DISCUSSION

A large body of evidence has established that cAMP plays a central role in the progression of cystic disease in patients with ADPKD and/or ADPLD by stimulating mural epithelial cell proliferation and secretion of fluid into cysts.[22] This has provided a strong rationale for therapies targeting cAMP and cAMP signaling. The ability to hormonally modulate cAMP signaling in a tissue/cell-specific manner provides a strategy that minimizes adverse effects on unaffected tissues or cells, which is obviously very important when considering treat-

Table 2. Main clinical and laboratory parameters at start and end of treatment period

	Octreotide			Placebo			*P* for Delta %
	Baseline	12 mo	Delta %	Baseline	12 mo	Delta %	
Creatinine, mg/dl	1.1 (0.43)	1.1 (0.47)	0.0 (0.12)	1.1 (0.52)	1.2 (0.62)	0.05 (0.12)	0.56
Iothalamate GFR[a], ml/min per 1.73 m^2	68.1 (26.53)	64.6 (25.66)	−5.1(15.46)	70.8 (28.08)	65.7 (26.40)	−7.2(13.21)	0.98
Aspartate aminotransferase, U/L	32.5 (13.77)	29.9 (8.61)	−2.4(23.66	28.6 (7.93)	29.1 (6.11)	5.2 (17.93)	0.23
Albumin, g/dl	4.3 (0.18)	4.3 (0.20)	0.4 (4.47)	4.4 (0.19)	4.4 (0.19)	1.1 (4.54)	0.64
Bilirubin, μmol/L	0.6 (0.26)	0.6 (0.24)	17.5 (61.72)	1.0 (1.52)	0.7 (0.40)	−3.7(34.09)	0.98
Alkaline phosphatase, U/L	92.5 (47.78)	99.0 (49.21)	9.8 (24.38)	107.5 (55.91)	101.4 (36.20)	−1.0(14.91)	0.29
Prothrombin time, INR	9.6 (0.71)	10.4 (0.66)	7.5 (4.98)	10.9 (5.22)	10.5 (1.59)	2.8 (15.61)	0.83
Sodium, mEq/L	139.0 (3.05)	138.0 (3.30)	−0.7(2.67)	139.2 (2.58)	139.2 (2.08)	0.0 (1.86)	0.12
Potassium, mEq/L	4.5 (0.46)	4.4 (0.35)	−1.5(8.61)	4.3 (0.44)	4.4 (0.43)	3.2 (15.85)	0.48
Blood glucose, mg/dl	93.4 (11.22)	102.4 (11.54)	10.2 (11.25)	93.6 (7.81)	95.3 (8.01)	2.0 (7.10)	0.02[b]
BUN, mg/dl	19.0 (7.23)	19.0 (7.37)	0.5 (19.72)	18.5 (7.66)	22.1 (10.50)	18.2 (21.40)	0.03[b]
Hemoglobin, g/dl	12.8 (1.24)	12.6 (1.38)	−1.1(5.31)	12.9 (0.97)	12.7 (1.14)	−1.4(5.84)	0.74
Liver volume, ml	5907.7 (2915.0)	5557.1 (2659.4)	−5.0(6.77)	5373.9 (3565.4)	5360.6 (3330.9)	0.9 (8.33)	0.048[b]
Kidney volume, ml[a]	1142.9 (826.9)	1128.5 (796.0)	0.25 (7.53)	803.0 (269.1)	873.5 (306.2)	8.61 (10.07)	0.045[b]

Data shown as mean (SD). BUN, blood urea nitrogen.
[a]Kidney volume/GFR: four transplant patients, eight ADPLD patients, and one patient with missing values were removed from this analysis.
[b]$P < 0.05$ octreotide *versus* placebo group.

ments for a chronic disease, such as ADPKD or ADPLD. For example, blocking the effect of vasopressin on the Gs protein-coupled receptor V2 in the kidney, thereby decreasing cAMP levels, inhibits renal cyst and kidney enlargement and improves renal function in four different genetic models of PKD, and clinical trials of vasopressin V2 receptor antagonists are in progress.[23–26] V2 receptor antagonists have no effect on PLD because V2 receptors are not expressed in the liver.

Somatostatin analogs acting on Gi protein-coupled receptors provide an alternative path to inhibit cAMP signaling in cholangiocytes, as well as in tubular epithelial cells, thus potentially improving PLD in addition to PKD. We have recently shown that octreotide significantly reduces cAMP levels and rates of cyst expansion in freshly isolated bile ducts from PCK rats grown in 3D culture.[19] Furthermore, intraperitoneal injection of octreotide to PCK rats for 4 to 16 weeks lowered cAMP levels in serum and freshly isolated bile ducts and decreased liver and kidney weights and cystic and fibrosis scores. These effects were deemed to be mediated by Gi protein-coupled SST2 receptors in cholangiocytes, as well as in the distal nephron and collecting duct. Somatostatin is also known to blunt secretin-induced cAMP accumulation and fluid secretion in cholangiocytes,[11–13] arginine vasopressin-induced cAMP accumulation and water permeability in collecting ducts and toad urinary bladder,[14–17] and secretin release.[10] Although vasopressin is the major adenylyl cyclase agonist in renal collecting ducts and distal nephron, secretin is the major adenylyl cyclase agonist in cholangiocytes. Secretin contributes to adenylyl cyclase-dependent urinary concentration along with vasopressin. Somatostatin also suppresses the expression of IGF-1, vascular endothelial growth factor, and other cystogenic growth factors and downstream signaling from their receptors.[18] Therefore, somatostatin analogs may reduce cAMP accumulation and cyst growth by multiple mechanisms.

We initiated a clinical trial of octreotide in patients with severe PLD encouraged by the results of our preclinical studies, our anecdotal clinical experiences, and the pilot study conducted by Ruggenenti *et al.*[21] The results of the clinical trial reported here show that administration of octreotide LAR for 1 year induced a moderate but significant reduction in liver volume, inhibited the growth of polycystic kidneys, and improved quality of life in patients with ADPKD and/or ADPLD, with low toxicity and few side effects. These results, in a group of genetically well-characterized patients with more severe PLD, treated for a more extended period of time, and with a positive outcome on quality of life, expand observations in two previous randomized, placebo-controlled trials. A crossover study of octreotide LAR (40 mg intramuscularly every 4 weeks) for 6 months in 12 ADPKD patients with advanced renal disease (mean total kidney volume 2435 ml, mean serum creatinine 1.9 mg/dl) showed that kidney volume increased by 2.2% ± 3.7% during active treatment compared with 5.9% ± 5.4% ($P < 0.01$) while on placebo.[21] A parallel-arm, double-blind trial of lanreotide (120 mg subcutaneously every 4 weeks) for 6 months in 54 patients with PLD (32 ADPKD and 22 ADPLD) showed that liver volume decreased 2.9%, from 4606 to 4471 ml, in the lanreotide group, whereas it increased 1.6%, from 4689 to 4895 ml, in the placebo group ($P < 0.01$).[27] In the 32 patients with ADPKD, total kidney volume decreased 1.5%, from 1000 to 983 ml in the lanreotide group, whereas it increased 3.4%, from 1115 to 1165 ml, in the placebo group ($P < 0.02$). A single subdomain score of the HRQoL questionnaire (SF-36), current health perception, improved significantly in patients treated with lanreotide ($P < 0.01$). The dose of lan-

Table 3. Patient reported outcomes using mean health-related quality of life scores

SF-36	Octreotide	Placebo
Physical functioning		
time 0	74.8 (21.96)	80.4 (23.73)
12 mo	77.0 (21.32)	82.1 (18.58)
P	0.4013	0.5668
Physical role		
time 0	59.8 (42.13)	76.8 (39.79)
12 mo	74.1 (35.00)	75.0 (41.60)
P	0.0381[a]	0.8555
Bodily pain		
time 0	67.8 (15.29)	65.5 (24.25)
12 mo	75.7 (19.02)	68.7 (25.51)
P	0.0158[a]	0.4653
General health		
time 0	55.9 (21.29)	58.0 (23.63)
12 mo	53.5 (17.32)	63.4 (23.96)
P	0.5265	0.1975
Vitality		
time 0	49.6 (21.81)	53.9 (25.96)
12 mo	54.4 (24.23)	54.6 (27.91)
P	0.2414	0.7801
Social functioning		
time 0	79.0 (19.56)	75.0 (27.30)
12 mo	82.9 (19.35)	81.3 (21.79)
P	0.2653	0.1309
Role emotional		
time 0	82.1 (32.05)	73.8 (37.39)
12 mo	91.4 (23.74)	81.0 (38.60)
P	0.2557	0.4874
Mental health		
time 0	76.0 (14.12)	75.4 (18.75)
12 mo	76.9 (16.54)	80.7 (18.76)
P	0.8734	0.2030
Standardized physical component scale		
time 0	42.6 (9.73)	46.0 (10.16)
12 mo	44.7 (10.00)	46.1 (9.51)
P	0.0563	0.9235
Standardized mental component scale		
time 0	50.8 (7.74)	48.4 (10.96)
12 mo	52.2 (8.03)	51.3 (11.15)
P	0.5049	0.0738

Data are mean (SD). Scored on a range of 0 to 100 (0 = worst imaginable, 100 = best imaginable). *P* (paired *t* test).
[a]$P < 0.05$ within group.

reotide used in this study is equivalent to 60 mg of octreotide (compared with 40 mg used in our study), but lanreotide has a lower affinity for the SST2 receptor than octreotide.

The administration of octreotide or lanreotide has been generally well tolerated, with mostly mild, predictable, and dose-dependent gastrointestinal side effects. A single patient in our study had pre-existing gallstones, and another with gallbladder sludge remained stable on octreotide therapy. Patients undergoing long-term octreotide treatment should be monitored for cholelithiasis symptoms or signs because this is a known complication.[28–30] One patient experienced alopecia and another symptomatic bradycardia, both of which are known adverse events associated with this treatment.[31–36] One patient developed steatorrhea and weight loss, also a recognized side effect.[37,38] A drawback of these treatments is the pain and granuloma formation associated with the injections. No significant fluctuations in cyclosporin levels were observed in the three renal transplant recipients taking octreotide with this medication.[39]

In summary, three independent randomized, placebo-controlled trials have had encouraging outcomes. Nevertheless, conclusions regarding safety and efficacy are limited by their short duration (6 to 12 months) and small number of subjects. Longer and larger clinical trials will be necessary to establish the long-term safety and efficacy of somatostatin analogs for ADPKD and/or ADPLD. Finally, combination therapies, including somatostatin analogs and other promising treatments, may in the future improve the efficacy and reduce the toxicity of emerging therapies for ADPKD and/or ADPLD.

CONCISE METHODS

Study Design

This was a single-center (Mayo Clinic, Rochester, MN), placebo-controlled, double-blind trial with a 2:1 randomization. It conformed to the principles of the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board. Patients were randomly assigned to receive octreotide or placebo and followed for 1 year. The primary end point (percent change in liver volume from baseline) as measured by magnetic resonance imaging (MRI) (or computed tomography [CT] in three patients, see below) at 12 months, and secondary end points were changes in total kidney volume, GFR, quality of life (QOL SF-36v2TM), and safety ascertained by reported adverse events, vital signs, and clinical laboratory tests. Novartis USA partially funded the study and supplied octreotide. The sponsor was not involved in the study design, in the enrollment of patients, or in the collection, analysis, data interpretation, or preparation of the manuscript. The manuscript was prepared by the authors and reviewed by the sponsor. The CONSORT guidelines were adhered to for all aspects of the conduct and manuscript writing of this clinical trial (www.consort-statement.org).

Eligibility

Men and women 18 years or older with a diagnosis of ADPKD or ADPLD, severe PLD defined as a liver volume >4000 ml or symptomatic disease due to mass effects from hepatic cysts, and who were not candidates or declining surgical intervention were eligible. Criteria for exclusion were inability to provide informed consent, women of childbearing potential unwilling to employ adequate contraception, serum creatinine concentration >3 mg/dl or dialysis dependency, symptomatic gallstones or biliary sludge, uncontrolled hypertension (SBP >160 mmHg; DBP >100 mmHg) or diabetes mellitus, cancer or major systemic diseases that could prevent completion of the planned follow-up or interfere with data collection or interpretation, and current or prior use of somatostatin analog within 6 months of enrollment or history of significant adverse reaction from a somatostatin analog.

Enrollment, Randomization, and Study Protocol

Enrollment took place from January 1, 2007, to May 19, 2008. Randomization (2:1) was performed to ensure that two-thirds of patients received Sandostatin LAR® (a long-acting depot form of octreotide that is administered intramuscularly once every 4 weeks) and one-third received placebo. Randomization assignment to octreotide or matching placebo treatment was independently managed by the research pharmacy. After verification of baseline eligibility data by the principal investigator and signature of written informed consent and consent for genotyping for *PKD1* and *PKD2* (and *PKRSCH* or *SEC63*), all women of childbearing age had a pregnancy test, and all patients were given a subcutaneous test dose of 100 μg of short-acting octreotide (Sandostatin®) and observed (vital signs) over a 4-hour period. The next day, after confirming tolerability of the test dose, they were given 40 mg of octreotide LAR in two 20-mg intramuscular injections (one in each buttock by nursing staff in the Center for Translational Science Activities [CTSA]) or placebo. Octreotide or placebo was continued at a dose of 40 mg by intramuscular injection every 28 $\pm$ 5 days. If needed because of side effects, the dose could be reduced to 30 or 20 mg. Patients returned for follow-up visits at 1, 4, 8, and 12 months for safety assessments, which included vital signs and physical examination and clinical laboratory parameters. MR or CT imaging of liver and kidneys was obtained at the baseline and 12-month visits.

Evaluation of Outcomes

Liver and kidney volumes were measured by MR or CT imaging. GFR was measured by clearance of iothalamate using a nonisotopic capillary electrophoresis-based method with monitoring of bladder emptying using ultrasound.[40]

Quality of life was assessed with the study form 36 SF-36 questionnaire administered at baseline and every 4 months thereafter. The SF-36 comprises nine minor domains (physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, change in health perception, and general health perception), which are summarized into a physical and mental component. Safety laboratory studies were performed on all patients at baseline, week 4, and then at 4-month intervals thereafter. All adverse events occurring during the study were recorded according to National Cancer Institute Common Toxicity Criteria http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (version 3.0).[41]

MRI Scans and Volumetric Measurements

MRI was performed using a 1.5-T magnet on a single scanner using a torso phased-array surface coil. No intravenous gadolinium was used. MRI protocols included single-shot fast spin-echo (SSFSE), steady-state free precession (SSFP), and 3D fat-saturated spoiled gradient echo (3D SPGR) sequences. 3D SPGR sequences were the most suitable for volume analysis in the majority of patients. All images were acquired in coronal planes. The protocol was modified specifically to include patients with very large liver or kidneys, which often extended into the pelvis. Field of view ranged between 35 and 48 cm, and slice thickness was 4 mm with 0-mm gap. All sequences covered from dome of diaphragm to the lowermost portion of the kidneys. All sequences were obtained during breath holds. If the entire liver and kidney(s) could not be covered during one breath hold, more than one set of images, with neighboring image sets overlapped by one slice, were acquired. Depending on liver/kidney sizes and patient's breath-holding capability, up to six sets of images were obtained for SSFSE and SSFP sequences, and up to two sets were obtained for 3D SPGR sequences.

In three patients, noncontrast CT was used for the analyses because MRI could not be performed: one claustrophobic individual, one oversized patient, and a third individual with a metallic ocular foreign body. Both initial and 1-year follow-up CTs were performed on a multi detector CT scanner using 5-mm thickness slices.

Image Analysis

Liver volumes (the primary end point) and total kidney volumes were measured at enrollment and at 1 year. The volumes of transplanted kidney and atrophic native kidneys were excluded from measurement in a total of four patients who underwent renal transplantation (three octreotide, one placebo). Eight patients with ADPLD (five on octreotide, three placebo) were excluded from the GFR and kidney volume analyses. One other ADPKD patient was excluded from the kidney volume analysis because of incomplete imaging coverage where kidney cysts extended deep into her pelvis.

Image analysis was performed by one of three image analysis specialists using a stereology approach implemented in the Mayo Clinic Analyze® software program http://www.mayo.edu/bir/Software/Analyze/Analyze.html.[42,43] Stereology is a statistical sampling technique used to estimate shape parameters (such as volume, area, and surface area) from images.[44] Three parameters (grid spacing in the x, y, and z direction) are required to conduct this analysis. To select appropriate parameters, four patients were selected for full segmentation. The entire liver and kidneys were segmented by hand. Different grid sizes with random offsets were systematically applied to the data, and the stereology-estimated volume was compared with the fully segmented volume. For liver volume calculation, a grid size of $20 \times 20 \times 2$ voxels was selected, which yielded an average of 0.34% measurement error. For kidney volume calculation, a grid size of $10 \times 10 \times 1$ voxels was selected, which yielded an average measurement error of 0.14%.

After completing each patient study, the marked images were verified by one of two radiologists who are specialized in abdominal MR imaging (B.F.K. and B.K.). The radiologists were blinded to patient treatment arm and timing of the scan for each subject (baseline or 1-year follow-up). Intrahepatic and intrarenal major vessels and porta hepatis vessels were included in all analyses. Kidney and liver volumes were obtained in one sitting for each individual patient. In some patients, the organ boundary of the liver and kidneys was difficult to delineate from that of the stomach, spleen, pancreas, and small and large bowel. In these patients, careful further correlation was made with the other sequences, including SSFSE and SSFP. Image analysis of CT images performed in three patients was similarly done.

Statistical Analysis

Sample size was determined on the basis of prior data in untreated patients suggesting a rate of kidney cyst growth of 5% $\pm$ 3% per year.[45] A 2:1 randomization design allowed as many patients as possible to receive octreotide. The goal was to detect at least a three-

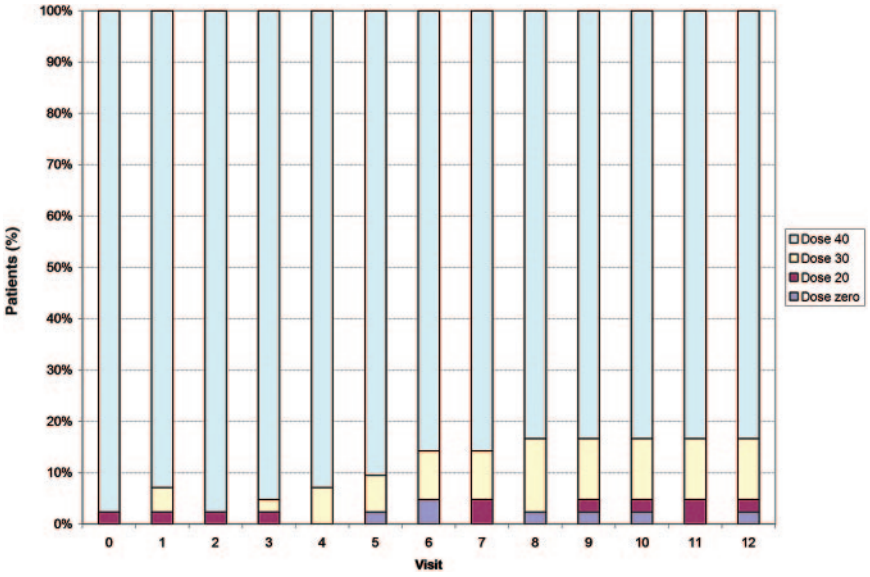

Figure 5. Most participants tolerate 40 mg of octreotide monthly. Dosing for all individuals assigned to octreotide treatment by dosing period. Blue, 40 mg; yellow, 30 mg; mauve, 20 mg; and violet, dose withheld.

percentage point decrease in the mean liver cyst growth rate when using octreotide compared with placebo. With 13 placebo and 26 octreotide patients (allowing for an 8% dropout rate: one placebo and two octreotide patients without end point data), we estimated that the study would have 82% power (alpha = 0.05, two-sided) to detect a three-percentage point difference.[46,47] Statistical analyses were performed using paired *t* test for within-group differences, also Wilcoxon rank-sum or Mann-Whitney tests were used to compare between-group differences. All reported *P* values were two sided, and *P* values <0.05 were considered statistically significant. For continuous parametric variables, values were reported as mean $\pm$ SD and range. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC), and PRISM 4 was used for graphical data.

Molecular Characterization of the Study Cohort

Genomic DNA from each of the study cohort probands was extracted, and both *PKD1* and *PKD2* genes were fully sequenced for each phenotypically defined ADPKD proband using previously described protocols.[48,49] The ADPLD genes, *SEC63* and *PRKCSH*,[3,4] were fully sequenced in study cohort probands with an ADPLD phenotype. Mutation-negative patients were sequenced for all four genes. Genotype was assigned on the basis of the molecular findings, when a likely pathogenic mutation was found in one of the four genes sequenced, or on the basis of the clinical findings, when no likely pathogenic mutation was found.

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DISCLOSURES

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