Long-term Effects of Octreotide on Liver Volume in Patients With Polycystic Kidney and Liver Disease

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BACKGROUND & AIMS: **Short-term studies have shown that somatostatin analogues are effective in patients with polycystic kidney and liver disease. We evaluated the long-term effects of long-acting release octreotide (octreotide LAR), a somatostatin inhibitor, vs placebo in these patients.**

METHODS: **We performed a controlled study of adults with polycystic kidney and liver disease (estimated glomerular filtration rate, 40 mL/min/1.73m^2 or more) at a single center in Italy. We analyzed data from 27 patients randomly assigned to groups given octreotide LAR (40 mg, n = 14) or placebo (n = 13) each month for 3 years. The primary outcome was absolute and percentage change in total liver volume (TLV), which was measured by magnetic resonance imaging at baseline, after 3 years of treatment, and then 2 years after treatment ended.**

RESULTS: **Baseline characteristics were similar between groups. After 3 years, TLV decreased by 130.2 ± 133.2 mL in patients given octreotide LAR (7.8% ± 7.4%) ($P = .003$) but increased by 144.3 ± 316.8 mL (6.1% ± 14.1%) in patients given placebo. Change vs baseline differed significantly between groups ($P = .004$). Two years after treatment ended, TLV had decreased 14.4 ± 138.4 mL (0.8% ± 9.7%) from baseline in patients given octreotide LAR but increased by 224.4 ± 331.7 mL (11.0% ± 14.4%) in patients given placebo. Changes vs baseline still differed significantly between groups ($P = .046$). Decreases in TLV were similar in each sex; the change in TLV was greatest among subjects with larger baseline TLV. No patient withdrew because of side effects.**

CONCLUSIONS: **In a placebo-controlled study of patients with polycystic kidney and liver disease, 3 years of treatment with octreotide LAR significantly reduced liver volume; reductions were maintained for 2 years after treatment ended. Octreotide LAR was well-tolerated. ClinicalTrials.gov number: NCT02119052.**

Keywords: ADPKD Volume; Cyst Growth; Somatostatin Analogue.

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Polycystic liver disease (PLD) is a rare disorder arbitrarily defined by presence of more than 20 liver cysts.[1] It may occur as a genetically distinct entity,[2] but it may also be observed in up to 94% of patients with adult polycystic kidney disease (ADPKD).[3] Symptoms of PLD, including early satiety, gastroesophageal reflux, pain, and dyspnea, are caused by massive cyst and liver enlargement and may affect health-related patient quality of life, even severely.[4] Major functional

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Abbreviations used in this paper: **ADPKD, adult polycystic kidney disease; ALADIN, A Long-acting Somatostatin Analogue on Disease Progression in Nephropathy due to Autosomal Dominant Polycystic Kidney Disease; cAMP, cyclic adenosine monophosphate; GFR, glomerular filtration rate; LAR, long-acting release; MRI, magnetic resonance imaging; PLD, polycystic liver disease; TLV, total liver volume.**

Most current article

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2015.12.049

complications include hepatic venous outflow obstruction, compression of the inferior vena cava, portal vein compression, or bile duct compression resulting in obstructive jaundice.[5] Cysts may also bleed or become infected, and cyst torsions or ruptures are rare but severe events.

For decades, treatment options relied on cyst aspiration and sclerotherapy or fenestration and even partial liver resection, which are invasive interventions that fail to affect cyst growth and disease progression.[6] Liver transplantation is the only rescue option for the most severe cases. Medical treatment of PLD has been limited to the use of analgesics for relief pain and antimicrobial agents to treat infected cysts or biliary tract.[6]

Several years ago, we observed by serial comparative computed tomography scan analyses that renal and even liver volumes did not change appreciably during 2 years of follow-up in an ADPKD patient with PLD who was on continued treatment with long-acting release octreotide (octreotide LAR) for a concomitant pituitary adenoma.[7] Octreotide is a somatostatin analogue with high affinity to somatostatin receptor subtype 2 and specific cytostatic activity against a variety of tumors.[8] Thus, the above observation, combined with evidence that both renal tubular and biliary tract cells express somatostatin receptors, in particular subtype 2, suggested that receptor activation by octreotide therapy might also help prevent or limit their uncontrolled proliferation in patients with ADPKD and/or PLD. Indeed, proliferation and secretion of renal tubular cells and cholangiocytes are modulated by adenosine 3′, 5′-cyclic monophosphate (cAMP),[9] and fluid secretion via secondary transport of chloride can be curtailed by somatostatin, as it is in the rectal gland of the shark.[10] Consistently, a pilot crossover study showed that 6-month treatment with octreotide LAR slowed renal volume growth in 14 patients with ADPKD[7] and even reduced liver volumes in the 12 patients with concomitant PLD.[11] Subsequent experimental studies found that cAMP levels are increased in kidneys and livers of rats with polycystic disease, and octreotide may reduce kidney and liver weights and mitotic indexes by reducing cAMP levels through interaction with specific tubular and biliary cells receptors.[12]

Thus, to assess the risk/benefit profile of long-term somatostatin inhibition, we took advantage of a single-center cohort of patients with ADPKD and concomitant PLD allocated to 3-year treatment with octreotide LAR or placebo in the context of a prospective, randomized, parallel group trial, A Long-acting Somatostatin Analogue on Disease Progression in Nephropathy due to Autosomal Dominant Polycystic Kidney Disease (ALADIN).[13] After treatment completion, study patients were maintained on active follow-up to evaluate residual treatment effect during a 2-year off-treatment period.

Methods

Study Design and Participants

ALADIN was an academic, independent, placebo-controlled, single-blind trial including 79 adult participants with ADPKD. They had an estimated (by Modification of Diet in Renal Disease study equation) glomerular filtration rate (GFR) $\geq$40 mL/min/1.73 m^2 and were referred to outpatient clinics of 5 hospitals in Italy.[13] After baseline evaluation, they were centrally randomized in a 1:1 ratio to a 3-year treatment period with octreotide LAR or placebo according to a computer-generated randomization list. Randomization was done by an independent investigator at the treatment assignment secretariat. The randomization sequence was created by using SAS (version 9.0; SAS Institute Inc, Cary, NC) and was stratified by center with random block size of 4 and 8. Study physicians and nurses were aware of the allocated group; participants and outcome assessors were masked to allocation. Thirty-nine ALADIN patients with concomitant PLD who were referred to the Università Federico II of Naples entered this single-center substudy (ClinicalTrials.gov, NCT02119052) that, in addition to the 3-year treatment period with octreotide LAR or placebo, also included a 2-year extension after treatment withdrawal (recovery). PLD was defined by the presence of at least 20 liver cysts.[1] Patients with concomitant systemic or renal parenchymal disease, diabetes, overt proteinuria (>1 g/24 h), urinary or biliary tract lithiasis or obstruction, more than 2 hemorrhagic or complicated cysts, cancer, or any condition that prevented the comprehension of the purposes and risks of the study were not considered eligible. Pregnant or lactating women or fertile women without effective contraception were also excluded.[13] The primary end point was the absolute and percent change in total liver volume (TLV) at the end of the treatment and recovery periods versus baseline.

The ALADIN trial and the present substudy conformed to the principles of the Declaration of Helsinki. The ALADIN trial was approved by the ethical committees of all involved centers including the ethical committee of the University Federico II, and all ALADIN participants provided written informed consent to study participation. ALADIN patients with concomitant PLD referred to the University Federico II provided written informed consent also to liver magnetic resonance imaging (MRI) evaluations. These evaluations were performed per center practice to monitor progression of liver involvement and were retrospectively analyzed for the purposes of the present single-center substudy. This study is reported according to the CONSORT guidelines. All authors of the article had access to the data. The corresponding authors had final responsibility for manuscript submission.

Procedures

Blood pressure was measured, and spot and 24-hour urine collections were sampled the morning after overnight fasting for laboratory assessments as previously detailed.[13] GFR was centrally measured by iohexol plasma clearance technique. Kidney and liver volumes were quantified by non–contrast-enhanced MRI (Supplementary Material). At randomization and every 28 days thereafter, participants received two 20-mg intramuscular injections of octreotide LAR or of 9% sodium chloride solution. Vital signs, physical examination, and laboratory variables were assessed at baseline and every 6 months. In substudy patients, liver MRIs were also evaluated at the end of the treatment and recovery periods.

Sample Size Estimation

Sample size was estimated for the main prespecified outcome variable, absolute TLV change at the end of the 3-year treatment period vs baseline, assuming a 2-group *t* test (two-sided) of the difference between octreotide LAR and placebo (Supplementary Material).

Statistical Analyses

All statistical analyses were done by modified intention-to-treat by using SAS (version 9.2) and STATA (version 13; Stata Corp, College Station, TX). Changes in TLV at 3 and 5 years and all other between-group effects were assessed by analysis of covariance, adjusted for baseline measurement. A linear mixed-model was used for longitudinal data. TLV was log-transformed before statistical analysis. Within-group comparisons were assessed by paired *t* tests, repeated-measures analysis of variance, or McNemar test. Correlations were tested with Pearson test. Data were expressed as mean (standard error), median (interquartile range), or number (%) unless otherwise specified. All *P* values were two-sided.

Role of the Funding Source

ALADIN costs were partially covered by the Polycystic Liver Foundation, which had no role in the study. Costs for liver volume measurements and evaluations at the end of the recovery period were covered internally. Octreotide LAR was supplied by Novartis Farma, Origgio (VA), Italy.

Results

The 39 ALADIN participants were enrolled from April 2006 to May 2008. Two patients did not fulfill the selection criteria for PLD, and 2 patients denied consent to enter the substudy. Thus, 17 patients allocated to octreotide LAR and 18 to placebo had baseline TLV evaluations. MRI image acquisitions were not adequate in 1 patient per group at baseline and in 2 patients on octreotide LAR and 3 patients on placebo at 3 years (Supplementary Figure 1). Moreover, 1 patient on placebo denied his consent to continue the study. Thus, 14 participants on octreotide LAR and 13 on placebo had complete MRI acquisitions for liver volume measurements at baseline and at the end of the treatment periods. All these patients had adequate image acquisitions at the end of the recovery period and were therefore available for primary efficacy analyses (Supplementary Figure 1).

At inclusion, patients showed diffuse multiple medium-size cysts in the context of largely preserved parenchyma (Gigot type 2 class)[14] with moderately enlarged TLVs. Their baseline characteristics, including TLV, were similar between treatment groups (Tables 1 and 2, Supplementary Table 1). Compliance with the study drug, evaluated by the ratio between administered/planned drug injections, exceeded 95% in both groups.

Liver Volumes

Treatment period. During the 3-year treatment period, TLV decreased in all 14 participants on octreotide LAR and in only 4 of the 13 participants on placebo ($P = .0002$, Fisher exact test). At 3 years, absolute TLV decreased significantly ($P = .003$) by 130.2 ± 133.2 mL (7.8% ± 7.4%) on octreotide LAR and increased by 144.3 ± 316.8 mL (6.1% ± 14.1 %) on placebo. Between-groups difference in TLV changes vs baseline was statistically significant ($P = .004$, analysis of covariance). Thus at the end of the treatment period, liver volumes were 357.7 ± 619.9 mL smaller in patients on octreotide LAR than in controls (Figure 1*A*, Table 2, Supplementary Table 2).

Recovery period. During the 2-year recovery period, TLV increased in 13 of the 14 participants initially on octreotide LAR and in 12 of the 13 participants originally on placebo. At 2 years after treatment withdrawal, absolute TLV increased by 115.8 ± 127.4 mL (9.7% ± 10.2 %) in patients originally randomized to octreotide LAR and by 80.1 ± 90.0 mL (4.9% ± 7.2%) in those originally on placebo (Figure 1*B*, Table 2, Supplementary Table 1).

Whole study period. At the end of the 5-year observation period, there was a net TLV increase as compared with baseline in 5 of the 14 participants originally randomized to octreotide LAR and in 12 of the 13 originally on placebo ($P = .004$, Fisher exact test). Thus, at 5 years after randomization, TLV decreased by 14.4 ± 138.4 mL (0.8% ± 9.7%) in patients originally on octreotide LAR and increased by 224.4 ± 331.7 mL (11.0% ± 14.4%) in those on placebo. Changes at 5 years as compared with baseline were significantly different between groups ($P = .046$; Figure 1*C*, Table 2, Supplementary Table 1). Actually, in the octreotide LAR group liver volume was relatively stable throughout the whole observation

Table 1. Baseline Characteristics of Study Participants According to Treatment Arms

	Octreotide LAR (n = 14)	Placebo (n = 13)
Demographic and main clinical and laboratory parameters		
Age (*y*)	30 ± 8	37 ± 8
	30 (25–36)	38 (31–41)
Male gender, n (%)	5 (36)	5 (38)
Height (*cm*)	168 ± 11	168 ± 8
	169 (156–178)	168 (164–175)
Weight (*kg*)	75 ± 21	76 ± 14
	71 (59–96)	78 (70–86)
Body mass index (kg/m^2)	26 ± 5	27 ± 4
	27 (22–30)	26 (25–30)
Systolic blood pressure *(mm Hg)*	117 ± 11	121 ± 12
	117 (110–127)	122 (110–133)
Diastolic blood pressure *(mm Hg)*	76 ± 10	78 ± 11
	75 (70–83)	77 (77–90)
Serum creatinine (*mg/dL*)	0.9 ± 0.3	1.1 ± 0.4
	0.8 (0.7–1.0)	1.1 (0.9–1.1)
GFR ($mL/min/1.73\ m^2$)[a]	96 ± 25	88 ± 30
	103 (92–109)	74 (69–117)
Urine proteins (*g/24 h*)	0.12 ± 0.10	0.18 ± 0.13
	0.14 (0.05–0.15)	0.14 (0.11–0.20)
Patients with concomitant medications, n (%)		
Angiontensin-converting enzyme inhibitors	5 (36)	9 (69)
Angiotensin receptor blockers	4 (29)	7 (54)
Statins	2 (14)	0 (0)

NOTE. Values are mean ± standard deviation and median (interquartile range) or N (%).
[a]By the iohexol plasma clearance technique.

period, whereas it progressively increased ($P = .037$, analysis of variance for linear trend) in the placebo group (Figure 2*A*). Thus, at the end of the study, TLV was 322.1 ± 604.9 mL smaller in patients originally randomized to octreotide LAR than in controls.

Changes in height-adjusted TLV paralleled the concomitant changes in TLV (Supplementary Table 1). For other outcome variables see Supplementary Material and Supplementary Table 1.

Treatment Effect According to Sex and Liver Volume

In the octreotide LAR group, during the 3-year treatment period TLV significantly and similarly decreased compared with placebo in both men and women ($P < .05$ for both comparisons; Table 2). The reduction was significant in both groups even after adjusting for age, height, and baseline volumes. In addition, in women TLV significantly decreased compared with baseline ($P < .05$) and then increased ($P < .01$) during the 2-year recovery period.

In the placebo group, TLV progressively increased in both men and women, and the increase appeared to be particularly fast in women (Table 2).

In the active treatment arm, TLV significantly and consistently decreased with octreotide and similarly recovered toward baseline values after treatment withdrawal in both subgroups with baseline TLV above or below the median (1477 mL and 1628 mL for the octreotide LAR and placebo groups, respectively) considered separately. However, in the control arm, liver growth was remarkably faster in patients with TLV above the median than in those with smaller livers. Thus, changes in TLV at the end of the treatment and recovery periods significantly differed between treatment arms in patients with larger TLV, but not in those with smaller livers to start with (Table 3, Figure 2*B* and *C*).

Adverse Events

Treatment was well-tolerated and was never discontinued. One patient with treatment-related asymptomatic cholelithiasis and one with acute cholecystitis recovered with pharmacologic treatment and completed the trial. For other events see Supplementary Material and Supplementary Table 3.

Discussion

In this 3-year prospective, randomized, placebo-controlled trial followed by a 2-year recovery period, we found that octreotide LAR therapy achieved a significant and clinically relevant protective effect against progressive liver volume growth and was safe and well-tolerated in ADPKD patients with relatively early liver involvement. During the placebo-controlled study period, liver volumes decreased in octreotide-treated patients

Table 2. Absolute Liver Volumes (mL) Throughout the Study in the Study Group as a Whole (Overall) and According to Gender

	Overall			Men			Women		
	Baseline	Treatment	Recovery	Baseline	Treatment	Recovery	Baseline	Treatment	Recovery
Octreotide LAR									
Mean ± standard deviation	1609.7 ± 501.2	1479.5 ± 470.9[a,b]	1595.3 ± 414.5[c,d]	2060.7 ± 503.9	1936.2 ± 473.7[d]	1978.0 ± 401.2	1359.1 ± 288.9	1225.7 ± 212.9[d,e]	1382.7 ± 237.4[c]
Median	1477	1280.0	1443.7	2395.5	2137.0	2181.0	1292.0	1147.0	1358.3
Interquartile range	1201.0–1935.9	1125.4–1656.2	1209.0–1896.0	1641.1–2435.5	1543.8–2235.2	1617.3–2247.9	1192.0–1560.4	1110.6–1252.2	1204.5–1409.1
Placebo									
Mean ± standard deviation	1693.0 ± 470.7	1837.2 ± 748.5	1917.3 ± 759.0[c,e]	1640.1 ± 123.5	1691.7 ± 158.4	1720.5 ± 192.0	1726.0 ± 606.5	1928.2 ± 960.0	2040.4 ± 959.9[f]
Median	1637.1	1764.7	1824.0	1595.6	1685.2	1643.0	1662.1	1821.9	1888.0
Interquartile range	1506.0–1812.0	1509.5–1890.0	1520.6–1991.1	1578.0–1696.4	1569.0–1804.0	1605.0–1842.6	1371.9–1958.3	1234.7–2238.3	1391.3–2421.6

[a] $P < .01$ vs baseline.
[b] $P < .01$ vs placebo.
[c] $P < .01$ vs treatment.
[d] $P < .05$ vs placebo.
[e] $P < .05$ vs baseline.
[f] $P < .05$ vs treatment.

but continued to increase in controls. The benefit was sustained over time, and at the end of the recovery period liver volumes were still significantly smaller in patients originally randomized to octreotide LAR than in those on placebo. In controls, TLVs progressively increased throughout the whole observation period, whereas in octreotide-treated patients, final liver volumes were still slightly reduced compared with baseline. Thus, 3 years of octreotide LAR therapy delayed disease progression by approximately 5 years.

Treatment was remarkably safe and well-tolerated. Consistent with evidence that only approximately 1% of patients with octreotide-induced gallstones have symptoms per year of treatment,[15] only 1 acute cholecystitis episode was observed, from which the participant recovered with medical therapy. Non-serious adverse events including diarrhea, flatulence, and abdominal pain were mild in nature and spontaneously waned shortly after randomization as expected, because the functional responses of the gastrointestinal tract and exocrine pancreas to somatostatin analogues are rapidly followed by local adaptation.[8]

Three previous studies evaluated the effects of 6-month treatment with lanreotide[16] or 6-month[11] or 1-year treatment[17] with octreotide LAR in patients with isolated or ADPKD-associated PLD. Notably, during active treatment, changes in liver volume ranged from a 9.7% increase to a 17.3% decrease. This wide data variability was most likely explained by the too short treatment period and possibly by a concomitant confounding effect of heterogeneous sex distribution and liver volumes.[18] Indeed, 2 studies included a large majority of women with very large livers,[16,17] and in the third study a majority of men had remarkably smaller livers.[11] Moreover, this inconsistent and relatively modest effect appeared to wane shortly after treatment withdrawal.[19] In sharp contrast with the above findings, here we observed that in all patients liver volumes decreased during 3-year octreotide LAR therapy, which actually slowed liver growth by almost 400 mL as compared with placebo, an effect that also translated into a significant volume reduction compared with baseline of about 120 mL.

The residual 10% liver volume reduction (corresponding to approximately 250 mL) we observed at 5 years in octreotide LAR–treated patients compared with controls provided the additional information that treatment effect can be sustained even after treatment withdrawal. Prolonged patient exposure might also explain why despite the small sample size, we were able to detect a significant treatment effect even in men, a finding that challenges the previous belief that the benefit of somatostatin analogues is restricted to women, in particular to younger women, possibly because of estrogen-induced changes in intracellular signaling pathways.[18] Of note, treatment-induced reduction in TLV was relatively independent of liver volumes at inclusion, whereas liver growth on placebo was remarkably faster in patients with

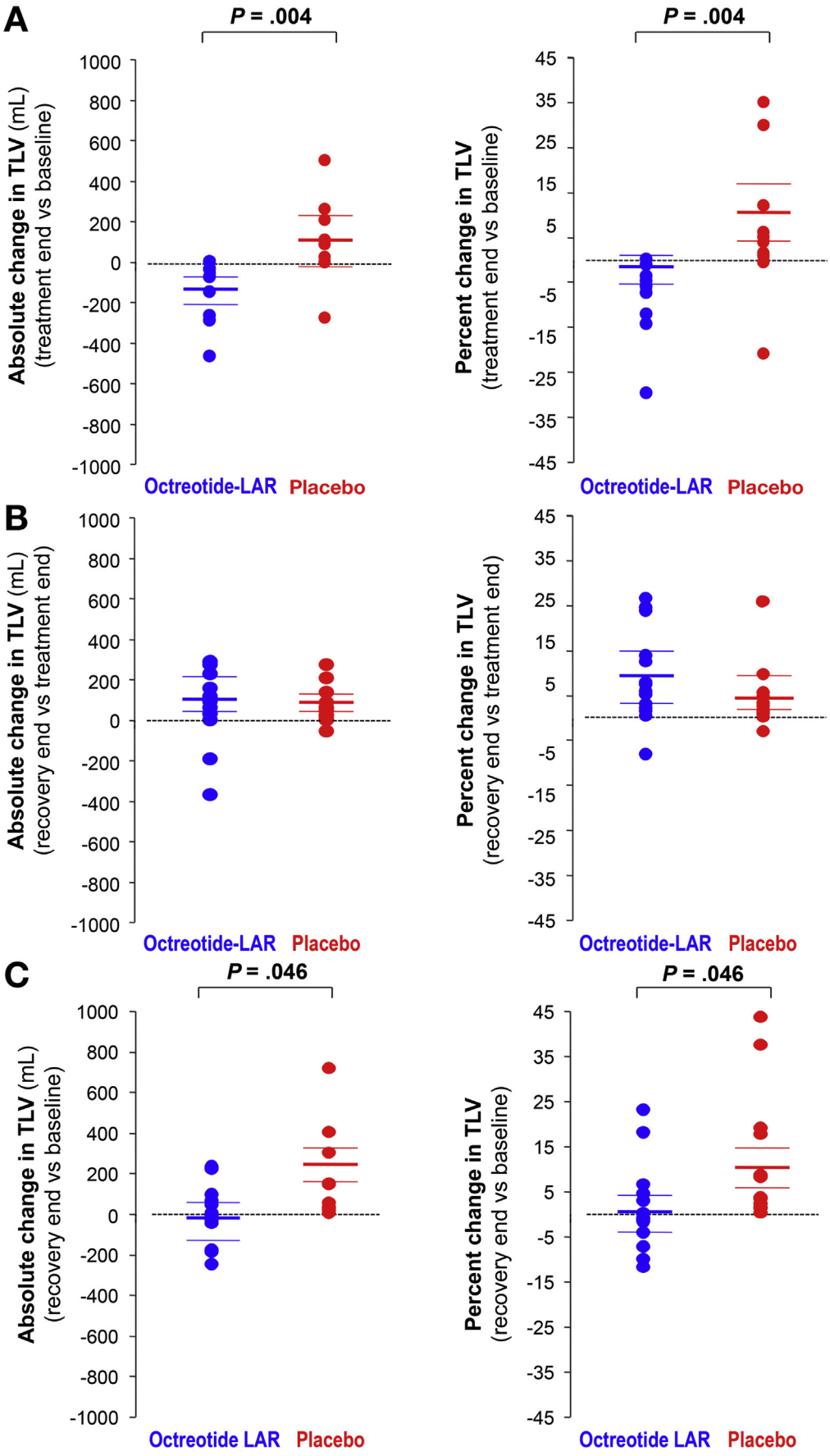

Figure 1. Individual and mean ± standard error of the mean absolute (*left panel*) and percent (*right panel*) changes in TLV at end of 3-year treatment with octreotide LAR (*blue circles*) or placebo (*red circles*) as compared with baseline (*A*), at end of 2-year recovery period as compared with end of 3-year treatment period (*B*), and at end of 5-year observation period as compared with baseline (*C*).

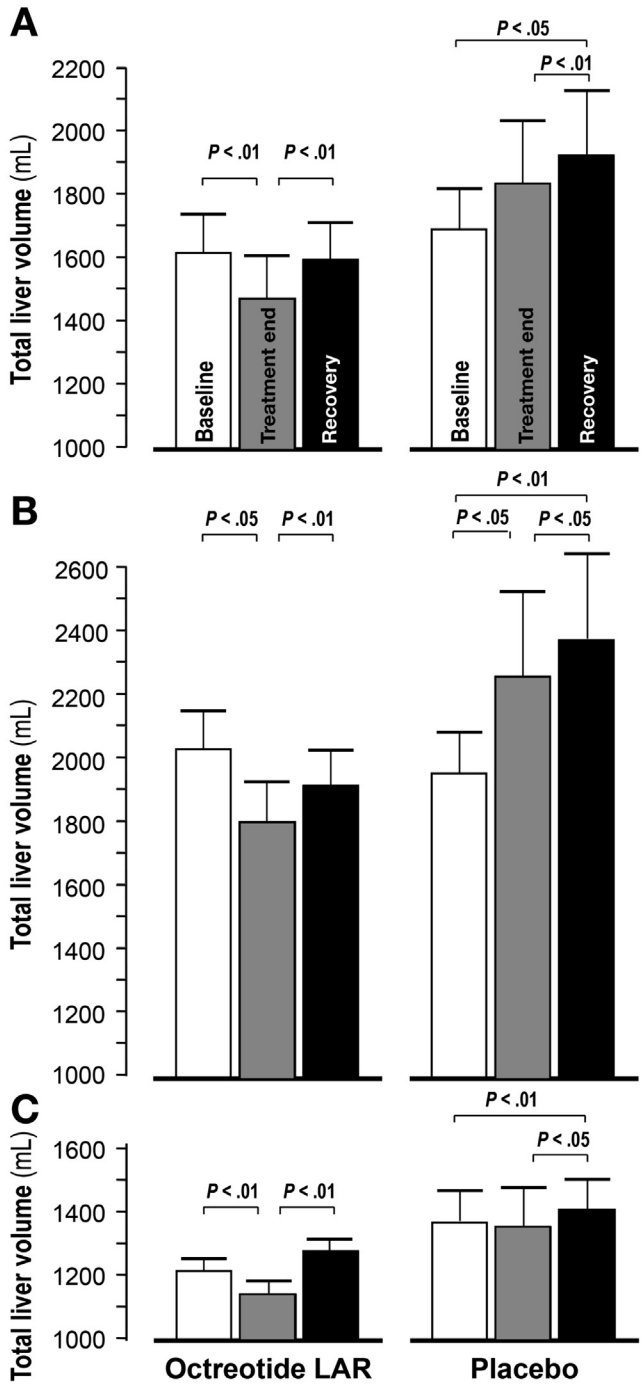

Figure 2. Mean ± standard error of the mean TLV at baseline, at end of 3-year treatment period, and at end of 2-year recovery period in the 2 treatment groups considered as whole (*A*) or according to baseline TLV above (*B*) or below (*C*) the median.

larger volumes. Consistently, the net benefit of octreotide LAR vs placebo was larger in patients with more severe hepatomegaly than in those with smaller livers to start with. These findings can be taken to suggest that somatostatin inhibition therapy may have a specific indication for both male and female ADPKD patients with liver volumes exceeding approximately 1500–1600 mL, whereas larger studies with longer follow-up are needed to assess in those with smaller livers whether early intervention may help prevent progression to more advanced and symptomatic stages of the disease.

The finding that liver volume reduction at 3 years exceeded by approximately 2-fold the volume reduction we previously observed during only 6-month treatment in a quite similar type of patients[11] suggested that treatment effect may be biphasic over time, with a faster short-term benefit followed by a sustained but to some extent slower effect in the long-term. This biphasic effect may be explained by 2 distinct and possibly overlapping mechanisms: (1) an immediate functional inhibition of cyst fluid secretion that may induce prompt cyst shrinkage and liver volume reduction, but which may wane shortly after treatment withdrawal,[19] and (2) a slower but progressive, time-dependent structural effect, possibly related to inhibited cholangiocyte proliferation and development and proliferation of new cysts,[12] which may substantially affect long-term disease progression. Consistently in the Tolvaptan Efficacy and Safety Management of ADPKD and Its Outcomes (TEMPO) trial, also the vasopressin inhibitor tolvaptan showed a more pronounced protective effect against kidney growth in the first year of treatment, which was explained by an acute decrease in the secretion of cyst fluid, followed by a steadily accumulating benefit during 3-year follow-up probably sustained by chronic inhibition of cyst-cell proliferation.[20] However, these effects are restricted to renal cysts.

Encouraging experimental data[21] and clinical observations[22] suggested that mammalian target of rapamycin inhibitors might also have a role in the treatment of ADPKD patients with PLD. However, 2 prospective, randomized clinical trials failed to detect any benefit of sirolimus or everolimus therapy on the progression of polycystic kidneys.[23,24] When added to recent evidence that everolimus combined with octreotide LAR did not further reduce polycystic liver volumes compared with octreotide LAR monotherapy,[25] these findings converge to indicate that mammalian target of rapamycin inhibitors do not provide any appreciable benefit to ADPKD patients with polycystic livers.

Thus, somatostatin analogues stand as the sole therapeutic option available for patients with PLD.

Limitations and Strengths

This was a post hoc analysis of liver MRI acquisitions recorded for clinical monitoring in a subgroup of the ALADIN cohort at a single center of the ALADIN network. However, baseline characteristics of ALADIN patients and of those included in the present study were quite similar, which reasonably excluded the possibility of substantial systematic errors. The per-center stratified randomization sequence also made it possible to achieve similar baseline characteristics between the 2 treatment groups, which reasonably limited the confounding effect

Table 3. Absolute Liver Volumes (mL) Throughout the Study According to TLV Larger or Smaller Than the Median Value in the Octreotide LAR (1477 mL) and Placebo (1628 mL) Groups

	TLV larger than median value			TLV smaller than median value		
	Baseline	Treatment	Recovery	Baseline	Treatment	Recovery
Octreotide LAR						
Mean ± standard deviation	2001.5 ± 412.4	1805.0 ± 470.1[a,b]	1902.1 ± 371.6[b,c]	1217.9 ± 126.5	1154.0 ± 110.5[d]	1288.4 ± 120.6[c]
Median	1935.9	1656.2	1896.0	1201.0	1147.0	1209.0
Interquartile range	1604.3–2435.5	1479.8–2235.2	1598.3–247.9	1186.1–1304.1	1098.3–1252.2	1189.2–1397.4
Placebo						
Mean ± standard deviation	1956.7± 478.2	2252.6 ± 777.3[a]	2354.0 ± 779.8[a,c]	1385.3 ± 262.2	1352.7 ± 310.5	1407.9 ± 272.6[a,c]
Median	1812.0	1890.0	1991.1	1443.6	1452.5	1472.5
Interquartile range	1687.0–2104.5	1804.9–2351.3	1842.6–2498.2	1362.7–1578.1	1073.9–1569.0	1358.3.3–1605.0

[a]$P < .05$ vs baseline.
[b]$P < .01$ vs placebo.
[c]$P < .01$ vs treatment.
[d]$P < .01$ vs baseline.

of unbalanced between-group distribution of prognostic factors. Analyses of covariance adjusted for baseline liver volumes and sensitivity analyses considering percent changes vs baseline provided consistent evidence that study findings were not appreciably confounded by the small differences in TLV observed between treatment arms at inclusion. The study was single-blind, but all study assessors involved in data recording and analyses, including analyses of liver MRI acquisitions, were blinded to treatment. As compared with patients of previous studies, including those with isolated PLD,[16,17] our patients had less severe liver involvement. Because they were largely symptom-free, we did not perform quality-of-life analyses. On the other hand, our present data prove the concept that early, preemptive intervention not only halts the growth of liver cysts but may even progressively reduce liver cyst volumes. This effect is sustained even after treatment withdrawal and in the long-term might hopefully prevent disease progression to more severe stages that might possibly be less responsive to treatment. Other strengths include the independent, fully academic nature of the study, the long treatment period, and the study extension with a long-term recovery phase. Moreover, the rigorous design and the use of gold standard techniques (MRI) for the measurement of liver volumes reduced random data fluctuations and allowed powerful analyses despite the relative small sample size. Finally, power analyses performed on the basis of treatment effect observed in a previous pilot study in a similar typology of patients[11] and of the actual number of available patients with liver MRI acquisitions provided the evidence that the substudy was adequately powered to test the working hypothesis. However, results of subgroup analyses, including those considering separately men and women or patients with different liver volumes at baseline, should be taken with caution because of the small sample size.

Conclusions

Altogether, our present data and previous findings from the ALADIN trial[13] converge to indicate that in ADPKD patients, octreotide LAR has a significant and clinically relevant curtailing effect on the growth of both liver and kidney cysts that is sustained over time. Because of its remarkably good safety and tolerability profile, even life-long,[26] this medication appears to be a viable option for chronic therapy of ADPKD patients with or without polycystic livers. Early treatment may help prevent progression to more severe and potentially irreversible stages of the disease that may require invasive interventions to palliate symptoms that severely impact patient quality of life. Whether alternate on/off treatment periods may help improve the cost/effectiveness of chronic somatostatin inhibition therapy is worth investigating.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.12.049.

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Acknowledgments
The authors thank the participants in the ALADIN study for their participation and contribution; the trial sub-investigators, the nephrologists, radiologists, and nurses of the participating centers for their invaluable assistance, the laboratory, medical imaging, and regulatory affairs staff, trial monitors, data managers and statisticians, and everyone at the Clinical Research Center for Rare Diseases Aldo e Cele Daccò of the IRCCS—Istituto di Ricerche Farmacologiche Mario Negri for their efforts in making this study possible. The authors thank Maurizio Spinello and Daniele Alberti (Novartis Italia) for continuous support for the study and a major contribution to all the administrative and operational aspects concerning the supply and distribution of the study drug. A list of members of the ALADIN study is in the Appendix in the Supplementary Material.

Conflicts of interest
The authors disclose no conflicts.

Funding
This research was partly funded by PKD Foundation, Kansas City, MO (grant number 01TRN07a).

Supplementary Material

Sustained Effects of Octreotide LAR in Patients With Adult Polycystic Kidney Disease With Polycystic Livers

ALADIN Trial Substudy With Two-Year Recovery

MRI acquisition. The non–contrast-enhanced MRI acquisition protocol overlapped with that of the Consortium for Radiological Imaging Studies of Polycystic Kidney Disease[1] and was set up for a 1.5 Tesla scanner. Coronal T1-weighted and T2-weighted series covering the entire liver were acquired in 1 breath-hold on a 1.5 Tesla MR Scanner (Gyroscan; Philips, Intera, The Netherlands) with slice thickness of 5 mm. Kidney volumes were evaluated as previously reported.[2] Livers were first manually outlined on T2-weighted MRI by a trained operator, masked to treatment, by using an interactive image editing software (Slicer 4.3.0, http://www.slicer.org/) that makes it possible to contour the liver simultaneously on the 3 views (sagittal, coronal, and axial) for higher precision. To improve liver tracing corresponding three-dimensional, T1-weighted images were visually inspected to resolve uncertainties in the regions where the liver and kidney were adjacent. Intrahepatic major vessels and porta hepatic vessels were included in all analyses. Outlines of the liver were obtained in 1 sitting for each individual case. After completing each patient study, the liver contours were independently verified by 2 radiologists specially trained in abdominal MRI; both were blinded to treatment. The corrected outlined masks of the liver were exported, and TLV was computed by multiplying the voxel count of the mask by voxel volume by using an in-house routine developed under IDL 7.0 (Exelis Visual Information Solutions, Boulder, CO) to obtain absolute TLV measures expressed in milliliters. In 10 ADPKD patients with PLD who had a repeat MRI scan 15 minutes after repositioning, the procedure was highly reproducible, with a concordance correlation coefficient $\geq$0.99.

Sample size estimation. Sample size was estimated for the main prespecified outcome variable, absolute TLV change at the end of the 3-year treatment period vs baseline, assuming a 2-group t test (two-sided) of the difference between octreotide LAR and placebo. On the basis of the pilot study[3] we assumed conservatively that a 6-monthly mean increase of 14 mL could be expected in the placebo group during 3-year follow-up with a concomitant decrease by 71 mL in the octreotide LAR treatment group. Assuming a common standard deviation of 71 mL, we calculated that a sample size of 12 evaluable participants per group would give the trial an 80% power to detect as statistically significant ($\alpha = 0{\cdot}05$, two-tailed test) the expected difference in TLV change between the 2 treatment groups. To account for a 15% dropout, we calculated that at least 28 participants had to be included to have 24 participants available for final analyses of the primary efficacy variable. On the basis of the above power analyses, we concluded that the 35 patients referred to the University Federico II who had been included and randomized in the ALADIN trial and fulfilled the criteria for inclusion in the PLD substudy provided an adequate power to test the effect of treatment with octreotide LAR on the main prespecified outcome variable.

Results

Other Outcome Variables

Throughout the whole 5-year observation period, blood pressure was stable and comparable between treatment groups. Glycosylated hemoglobin levels transiently increased during active treatment, but changes in glycosylated hemoglobin levels throughout the study period never differed between groups. As expected, serum creatinine increased progressively in both groups, whereas changes in height-adjusted liver volumes paralleled the concomitant changes in TLVs, with a significant decrease during octreotide LAR treatment and a progressive increase in controls (Supplementary Table 1).

Adverse Events

One asymptomatic cholelithiasis that was accidentally discovered at a 3-year MRI examination and 1 acute cholecystitis were reported as treatment-related adverse effects. Patients recovered from both events fully with pharmacologic treatment, and both participants completed the study as planned. Other non–treatment-related serious adverse events were rare and similarly distributed between groups (Supplementary Table 2).

As previously reported in the ALADIN trial, there were some non-serious adverse events possibly related to octreotide LAR, including abdominal discomfort, flatulence, and sporadic diarrhea, which were mild, and participants recovered spontaneously within 1 month after randomization. Two hypoglycemic episodes were also reported in 2 participants on octreotide LAR. In no case did the study treatment have to be withdrawn or back-titrated even transiently.

Appendix

ALADIN-PLD Study Organization

Members of the ALADIN-PLD Substudy Organization were as follows (all in Italy unless otherwise noted): Principal investigator: A. Pisani (Naples); Study coordinator: M. Sabbatini (Naples); Coordinating center: P. Ruggenenti, G. Remuzzi — Mario Negri Institute for

Pharmacological Research, Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Villa Camozzi, Ranica (Bergamo); Participating center: A. Pisani, B. Visciano, M. Amicone, R. Dipietro, G. Mozzillo, E. Riccio, R. Rossano, M. Sabbatini, L. Spinelli, M. Santangelo (Naples); Monitoring, drug distribution and pharmacovigilance (Mario Negri Institute): N. Rubis, O. Diadei, W. Calini, A. Villa, M. Sabatella (Ranica); Database and data validation (Mario Negri Institute): B. Ene-Iordache, S. Carminati, D. Martinetti (Ranica); Randomization (Mario Negri Institute): G. A. Giuliano (Ranica); Data analysis (Mario Negri Institute and Federico II University): A. Perna (Ranica); R. Liuzzi (Naples); Medical imaging (Mario Negri Institute and Federico II University): A. Remuzzi (Ranica) and M. Imbriaco, A. Prinster, M. Altiero (Naples); Regulatory affairs (Mario Negri Institute): P. Boccardo, S. Peracchi (Ranica).

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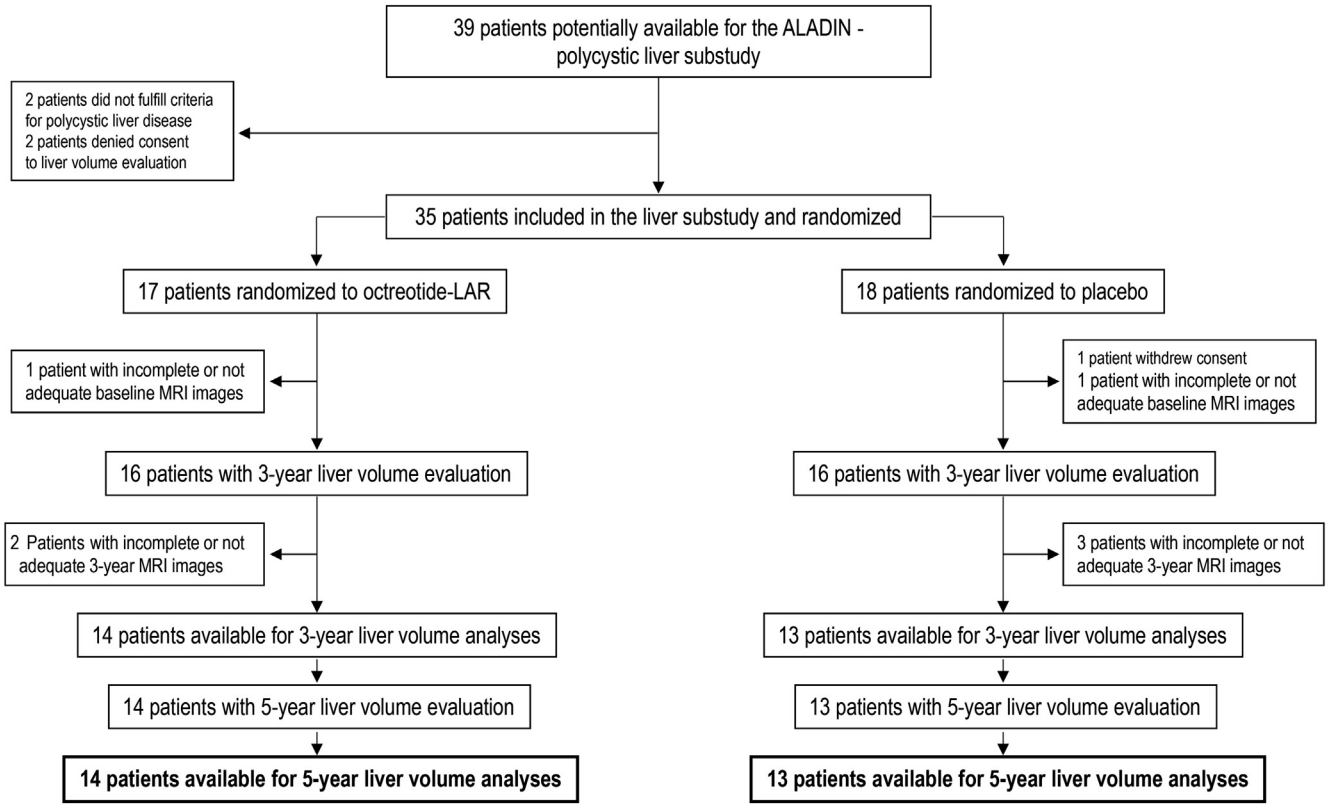

Supplementary Figure 1. Trial profile.

Supplementary Table 1. Main Clinical and Laboratory Parameters at Baseline, 3 Years After Randomization (Treatment), and 2 Years After Treatment Withdrawal (Recovery)

	Octreotide LAR			Placebo		
Parameter	Baseline	Treatment	Recovery	Baseline	Treatment	Recovery
Mean blood pressure, *mmHg*	89.8±9.6	90.0±6.4	89.2±5.6	92.5±11.1	90.2±6.9	94.4±6.0
Aspartate aminotransferase, *U/L*	22.3±10.2	20.2±6.4	18.2±3.4	17.8±3.5	18.4±4.8	17.5±4.4
Bilirubin, *mmol/L*	0.73±0.42	0.59±0.24	0.41±0.15[a,b,c]	0.49±0.20	0.47±0.17	0.45±0.15
Serum albumin, *g/dL*	4.7±0.3	4.8±0.3	4.5±0.4[b]	4.6±0.5	4.6 ± 0.4	4.7±0.5
Alkaline phosphatase, *U/L*	52.0±14.3	61.2±19.4	55.4±11.7	52.5±9.7	50.8±11.9	62.02±21.7[e]
Glucose, *mg/dL*	74.8±10.3	78.8±8.1	84.6±5.4[d]	78.8±8.6	79.8±9.4	87.5±6.5[a,e]
HbA1C, %	5.3±0.3	5.6±0.4[a]	5.3±0.3[e]	5.5±0.3	5.6±0.3	5.6±0.4
Cholesterol, *mg/dL*	178.4±26.3	185.7±32.0	183.7±19.6	167.5±39.9	163.7±28.5	170.2±21.7
Triglycerides, *mg/dL*	124.6±71.0	123.5±62.0	109.9±22.9	94.9±33.0	90.8±37.5	93.8±15.8
Hemoglobin, *g/dL*	14.3±1.3	13.1±1.1[d]	13.1±1.1[a]	13.7±1.4	13.1±1.0[a]	13.0±1.1
Sodium, *mEq/L*	140.1±2.0	140.8±1.5	140.4±3.5	141.5±2.5	141.0±1.5	140.4±.2.9
Potassium, *mEq/L*	4.2±0.3	4.2±0.5	4.4±0.5	4.4±0.4	4.3±0.54	4.5±0.4
Serum creatinine, *mg/dL*	0.94±0.31	1.16±0.64	1.41±1.06[d,e]	1.10±0.40	1.31±1.1[a]	1.66±1.06[d,e]
Ht-TLV, *mL*	949.1±249.2	872.6±235.3[c]	943.8±203.8[f]	1008.3±286.7	1096.2±458.8	1143.7±466.1

NOTE. Data are expressed as mean±SD.
Ht-TLV, height adjusted total liver volume.
[a]$P < .01$ versus baseline.
[b]$P < .01$ versus treatment.
[c]$P < .01$ versus placebo.
[d]$P < .05$ versus baseline.
[e]$P < .05$.
[f]$P < .05$.

Supplementary Table 2. Absolute and Percent Changes in Liver Volumes Throughout the Study

	Absolute changes in liver volumes (mL)			Percent changes in liver volumes		
	Treatment vs baseline	Recovery vs treatment	Recovery vs baseline	Treatment vs baseline	Recovery vs treatment	Recovery vs baseline
Octreotide LAR						
Mean ± standard deviation	–130.2 ± 133.2[a,b]	115.8 ± 127.4[a]	–14.4 ± 138.4[c]	–7.8 ± 7.4[b]	9.7 ± 10.2	0.8 ± 9.7[c]
Median	–83.3	112.3	–21.3	–5.9	7.2	–1.4
Interquartile range	–160.3 to –51.9	43.5–238.2	–57.5 to 54.2	–7.5 to –4.0	2.8–14.5	–4.6 to 4.2
Placebo						
Mean ± standard deviation	144.3 ± 316.8	80.1 ± 90.0[d]	224.4 ± 331.7[e]	6.1 ± 14.1	4.9 ± 7.2[e]	11.0 ± 14.4[f]
Median	67.0	59.3	47.4	3.7	2.3	3.1
Interquartile range	–5.2 to 193.6	28.8–101.1	18.0–294.7	–0.6 to 11.4	1.8–5.3	1.0–17.4

[a] $P < .01$ vs baseline.
[b] $P < .01$ vs placebo.
[c] $P < .05$ vs placebo.
[d] $P < .01$ vs treatment.
[e] $P < .05$ vs treatment.
[f] $P < .05$ vs baseline.

Supplementary Table 3. Serious Adverse Events According to Treatment Group

Event	Octreotide LAR (n = 14)	Placebo (n = 13)
Cholelithiasis	1 (7.1)	0
Acute cholecystitis	1 (7.1)	0
Gastroenteritis	0	1 (7.7)
Hepatic cyst hemorrhage	1 (7.1)	0
Nephrolithiasis	0	1 (7.7)
Renal cyst hemorrhage	1 (7.1)	1 (7.7)
Urinary tract infection	1 (7.1)	1 (7.7)
Intracranial aneurysm	1 (7.1)	0
Hypertensive crisis	0	1 (7.7)

NOTE. Data are shown as number and percent of patients with adverse events.