Somatostatin analog therapy for severe polycystic liver disease: results after 2 years

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Abstract

Background. We showed in a randomized double-blinded
placebo-controlled clinical trial that octreotide long-acting
repeatable depot.® (OctLAR®) for 12 months reduces
kidney and liver growth in autosomal dominant polycystic
kidney patients with severe polycystic liver disease (PLD)
and liver growth in patients with severe isolated PLD. We
have now completed an open-label extension for one
additional year to assess safety and clinical benefits of con-
tinued use of OctLAR for 2 years (O→O) and examined
drug effect in the placebo group who crossed over to
OctLAR in Year 2 (P→O).

Methods. The primary end point was change in total
liver volume (TLV) measured by magnetic resonance
imaging (MRI); secondary end points were changes in
total kidney volume (TKV) measured by MRI, glomerular
filtration rate (GFR), quality of life (QOL), safety, vital
signs and laboratory parameters.

Results. Forty-one of 42 patients received OctLAR ($n =$
28) or placebo ($n = 14$) in Year 1 and received OctLAR in
Year 2 (maximum dose 40 mg). Patients originally ran-
domized to placebo (P→O) showed substantial reduction
in TLV after treatment with OctLAR in Year 2 (Δ% −7.66
± 9.69%, P = 0.011). The initial reduction of TLV in the
OctLAR group (O→O) was maintained for 2 years (Δ%
−5.96 ± 8.90%), although did not change significantly
during Year 2 (Δ% −0.77 ± 6.82%). OctLAR inhibited
renal enlargement during Year 1 (Δ% +0.42 ± 7.61%) in
the (O→O) group and during Year 2 (Δ% −0.41 ± 9.45%)
in the (P→O) group, but not throughout Year 2 (Δ%
+6.49 ± 7.08%) in the (O→O) group. Using pooled ana-
lyses of all individuals who received OctLAR for 12
months, i.e. in Year 1 for O→O patients and Year 2 for
P→O patients, average reduction in TLV was −6.08 ±
7.58% (P = 0.001) compared to net growth of 0.9 ±
8.35% in the original placebo group. OctLAR-treated
individuals continued to experience improvements in
QOL in Year 2, although overall physical and mental
improvements were not significant during Year 2 com-
pared to Year 1. Changes in GFR were similar in both
groups.

Conclusion. Over 2 years, OctLAR significantly reduced
the rate of increase in TLV and possibly the rate of in-
crease in TKV.

Keywords: chronic kidney disease; kidney volume; liver cyst; polycystic
kidney disease; somatostatin analogs

Introduction

Preclinical studies in the PCK rat (a recessive model of
polycystic kidney and liver disease) showed that the
somatostatin analog octreotide reduces 3′, 5′-cyclic adeno-
sine monophosphate (cAMP) levels in kidney and bile
ducts and slows the progression of hepatorenal cystogen-
esis [1]. We previously completed a double-blinded, ran-
domized placebo-controlled clinical trial (NCT00426153)
using octreotide long-acting repeatable depot® (OctLAR)
over 1 year in 42 patients with severe polycystic liver
disease (PLD) due to autosomal dominant PLD (ADPLD)
or autosomal dominant polycystic kidney disease
(ADPKD) [2]. Two other prospective clinical trials have
shown similar positive effects of somatostatin analogs in
ADPLD and ADPKD [3–5]. A few other published
reports relating to the use of somatostatin analogs further
substantiate these observations [6–8]. All these studies are
limited by small numbers of enrolled patients with a short
follow-up of 6–12 months. In order to evaluate whether
somatostatin analog therapy retards liver and kidney
growth beyond 1 year, our protocol design included a
second year of open-label active therapy with OctLAR.
Here, we report the effects of OctLAR in patients who
were randomized to the placebo group during 1 year and
the effects of two continuous years of OctLAR treatment.

Materials and methods

Study design

This was a single-center (Mayo Clinic, Rochester, MN), placebo-controlled double-blinded trial with a 2:1 randomization which continued into the second year as an open-label extension study. All participants signed informed consents. The rationale, design and implementation of this trial (NCT00426153) have been described in detail [2]. 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 OctLAR or placebo in the first year of the study and all participants were offered OctLAR in Year 2. 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 and 24 months, and secondary end points were changes in total kidney volume (TKV), glomerular filtration rate (GFR), quality of life (QOL SF-36v2TM) and safety ascertained by reported adverse events, vital signs and clinical laboratory tests. Novartis US supplied OctLAR and partially funded the study.

Novartis provided logistical support during the trial. The investigators prepared the statistical analysis plan and all analyses were performed by the Mayo Clinic. The manuscript was prepared by Drs Hogan and Masyuk. Novartis was permitted to review the manuscript and suggest changes, but the final decision on content was exclusively retained by the authors. The CONsolidated Statement Of Reporting Trials 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 with a diagnosis of ADPKD (meeting Ravine's criteria) or ADPLD (defined by the criteria described by Reynolds *et al.*), 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 (Figure 1) [9, 10]. Patients had to be willing to travel to Mayo Clinic, Rochester, MN. 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 (systolic blood pressure >160 mmHg and diastolic blood pressure >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.

Study protocol

Enrollment took place from 1 January 2007 to 19 May 2008. This study was an open-label extension through Year 2, preceded by a 2:1 randomized, double-blinded placebo-controlled trial. After 12 months, all 41 patients continued (O→O) or crossed over to OctLAR (P→O). The drug was dispensed at 4-month intervals at the Mayo Clinic Research Pharmacy. Phone follow-up by a study coordinator was done monthly, and adverse events were reported to the study coordinator at each call or as needed. The study coordinator contacted patients monthly to confirm drug and dose administration. If there were drug side effects during a phone visit, a decision was made by the study team to reduce next injection dose by 10 or 20 mg (only needed in one case in the P→O group). All patients were evaluated by the principal investigator (MCH) or co-investigator (VET) at initial evaluation, and following randomization, then at 1 month and every 4 months, except for the Month 20 visit as there were few medical issues and all participants had safety assessments which included a physical examination, vital signs and clinical laboratory parameters (aspartite aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, electrolytes, blood urea nitrogen, creatinine, fasting glucose, complete blood count, activated partial thromboplastin time, prothrombin time). MR or CT imaging of liver and kidneys was obtained at the baseline, 1 and 2 years visits. All medications commenced were checked for drug interactions by the study team using Micromedex®.

At baseline, all women of child-bearing age had a pregnancy test, and all patients were required to use contraception or were post-menopausal. They were given a subcutaneous test dose of 100 mcg of short-acting octreotide (Sandostatin®) and observed (vital signs) over a 4-h period at time zero, except one patient who had previously received OctLAR. The following day, after confirming tolerability of the test dose, they were given 40 mg of OctLAR in two 20 mg intramuscular injections (one in each buttock) by nursing staff. Side effects were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria [11].

Outcome measures

The primary goals of the second year of follow-up in our study were to analyze the change in total liver volume (TLV) during the second year of continued OctLAR and to analyze the effects of OctLAR in the placebo group after crossing over to OctLAR in the second year. The secondary outcomes were to assess in a similar manner the effects of OctLAR on total kidney volume TKV, GFR measured by iothalamate clearance and QOL, as well as its safety and toxicity over 2 years of treatment.

The primary end point (percent change in TLV from baseline) as measured by MRI (or CT in four subjects, see below) and the secondary end points [changes in TKV, GFR, QOL (QOL SF-36v2TM)] were compared at Years 1 and 2 to that at baseline. We also assessed the safety ascertained by reported adverse events, vital signs and clinical laboratory tests.

MRI scans and volumetric measurements

All volumetric measurements were performed by the same blinded independent investigators and were compared with the baseline and Year 1 data as previously described. Repeat MRIs of liver and kidneys (or CT scan where MRI contraindicated or not possible) to reassess organ volume were performed in all participants at the end of Year 2. Absolute and percent changes in TLV and TKV at baseline, 1 and 2 years were assessed. To ensure that these two different imaging techniques are in agreement, liver and kidney volumes were calculated from CT and MRI in 10 patients who had CT and MRI performed within 15 days of one another. Measurements were calculated with Analyze® software and results were compared using Pearson's correlation coefficient. Excellent correlation was found between the volumes measured from CT and MRI images ($r = 0.998$). Of the original enrolled group, one individual in the OctLAR treatment group was withdrawn after Year 1; therefore his data were excluded in the second year analysis, and another had incomplete coverage of liver volume—therefore their TLV could not be used for the second year analysis, leaving 40 patients with analyzable TLV data at the end of Year 2. In four cases, non-contrast CT was used for the analyses because MRI could not be performed—one claustrophobic individual, one oversized patient, a third individual with a metallic ocular foreign body and a fourth, who was hospitalized with abdominal pain. Both initial and second year follow-up, CTs were performed on a multi-detector CT scanner using 5-mm thickness slices.

Image analysis

TLVs and TKVs were measured at enrollment, Year 1 and Year 2. The volumes of transplanted kidney and atrophic native kidneys were excluded from measurement in a total of four patients (three receiving OctLAR and one receiving placebo) who underwent renal transplantation. Eight patients with ADPLD (four receiving OctLAR and four receiving placebo) were excluded from the GFR and kidney volume analyses. One other ADPKD patient was excluded from the TKV analysis due to incomplete imaging coverage.

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 [12, 13].

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.J.K.). The radiologists were also 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. TKVs and TLVs were obtained in one sitting for each individual case. In some cases, 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 cases, careful further correlation was made with the other sequences, including single-shot fast-spin echo and steady state free precession. Image analysis of CT images performed in four patients was similarly done.
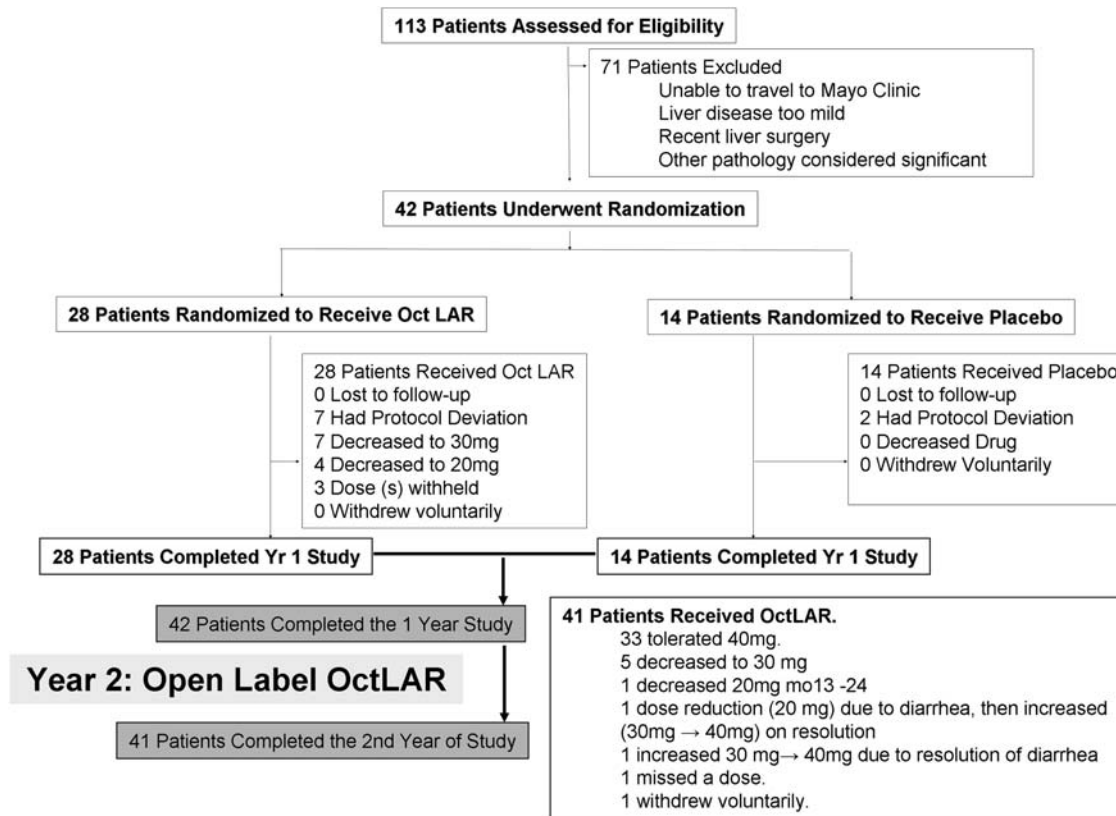
Fig. 1. Study flow diagram: 41 patients were enrolled in the second year (open-label extension). One individual withdrew voluntarily due to steatorrhea associated with OctLAR after completing the first year.

Patient genotypes

Mutation analysis was performed as previously described [2]. Thirty-two patients had ADPKD: of these 25 had a *PKD1* mutation, 6 had a *PKD2* mutation and in 1 patient, no mutation was detected. Eight patients had ADPLD: of these, four had a *PRKCSH* mutation, one had a *SEC63* mutation and in three patients, no mutation was detected. ADPKD and ADPLD genotypes and phenotypes were equally distributed between the OctLAR and placebo groups.

Statistical analysis

Statistical analyses were performed using paired *t*-test to compare differences within groups. All reported P-values were two-sided, and P-values <0.05 were considered statistically significant. Non-parametric tests gave similar conclusions (not shown). For continuous parametric variables, values were reported as mean ± SD and range. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC) and PRISM 5 used for graphical data.

Results

Baseline characteristics

A total of 42 patients were enrolled and randomized in this trial, of these: 28 in the OctLAR treatment arm and 14 in the placebo arm (Figure 1). Baseline demographic, socioeconomic and medical characteristics were similar between the two randomized groups [2].

Retention

Forty-one of 42 patients participated in the Year 2 open-label extension study (Figure 1). One patient withdrew from the study after the first year due to steatorrhea. Twenty-seven of the original OctLAR group (*n* = 28 in Year 1) received OctLAR at 40 mg every 28 days or maximum tolerated dose (O→O). The placebo group (*n* = 14) was crossed over to receive the same regimen of OctLAR (P→O). All forty-one patients completed the second year open-label extension. One patient from the original OctLAR group had incomplete coverage of liver volume by the end of Year 2; therefore, TLV was analyzed in 40 patients.

Main outcome

Liver volumes. In patients that were randomized to placebo (*n* = 14), TLV increased by 0.9 ± 8.35% compared to baseline during first year of the clinical trial (Table 1). In Year 2, after these patients were crossed over to OctLAR, TLV decreased from 5360 ± 3331 mL (assessed by the end of Year 1) to 4952 ± 3344 mL (assessed by the end of Year 2) or by −7.66 ± 9.69% (P = 0.01) (Table 1). Among these patients, several individuals experienced more substantial (10–25%) cumulative reductions of TLV after treatment with OctLAR (Figures 2 and 3).

In patients that received OctLAR during Year 1 (*n* = 26), TLV decreased from 5984 ± 2961 mL (assessed at enrollment) to 5628 ± 2720 mL at the end of Year 1 and 5649 ± 2870 mL at the end of Year 2 (Table 2) or −5.23 ± 6.22% in Year 1 (P = 0.0002) and −0.77 ± 6.82% (P =

Table 1. Changes in liver and kidney volumes and renal function in subjects randomized to placebo (P) for Year 1, all whom crossed over to octreotide (O) for Year 2[a]

	Duration of treatment (year)			Change on P Δ Year 0, Year 1	Change on O Δ Year 1, Year 2
	0	1	2		
Total liver volume, cc					
N	14	14	14		
Mean (SD)	5374 (3565)	5360 (3331)	4952 (3344)	−13.31 (603.28)	−408.40 (775.04)
% Change (SD)				0.90 (8.35)	−7.66 (9.69)
P-value				0.69	0.011
TKV, cc w/o ADPLD					
N	8	8	8		
Mean (SD)	803 (269)	874 (306)	885 (355)	70.50 (84.15)	11.55 (82.38)
% Change (SD)				8.61 (10.07)	0.41 (9.45)
P-value				0.046	0.90
GFR, mL/min/1.73BSA w/o ADPLD					
N	9	9	9		
Mean (SD)	70.8 (28.1)	65.7 (26.4)	62.6 (29.0)	−5.11 (7.56)	−3.11(8.42)
% Change (SD)				−7.2 (13.2)	−6.3 (13.0)
P-value				0.14	0.19

[a]P-values for Year 2 versus Year 1 in liver volume, renal volume, GFR (assessed as a percent change) are 0.061, 0.16 and 0.89, respectively. Paired t-test was used for statistical analysis within group, e.g. for TLV, 14 individual percent changes were used, not the overall mean percent change at each time point. There was one incomplete kidney volume at 0 and 1 year. Wilcoxon non-parametric tests revealed similar P-values.
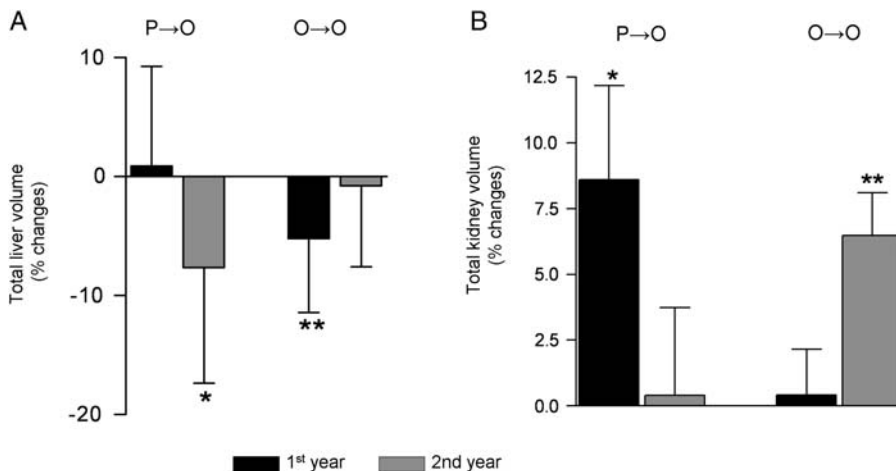

Fig. 2. Effects of OctLAR therapy on the TLV and TKVs as represented by percentage changes (mean ± SD) during Year 1 (from baseline to Month 12) and Year 2 (mean ± SD) (from Month 12 to Month 24). (**A**) Percentage change in TLV (mL) (mean ± SD) in patients who received placebo (P) for 1 year and then crossed over to OctLAR during Year 2 (O) (P→O) or receiving continuous OctLAR treatment for 2 years (O→O). *P = 0.011 compared to TLV assessed by the end of Year 1; **P = 0.002 compared to baseline. (**B**) Percentage change (mean ± SD) in TKV on placebo and then crossed over to OctLAR during Year 2 (P→O) or receiving continuous OctLAR treatment for 2 years (O→O). *P = 0.05 compared to baseline; **P = 0.008 compared to TKV assessed by the end of 1 year.

0.57) in Year 2. Therefore, reduction was maintained but did not change significantly during Year 2 (Figure 2A and Table 2). When we analyzed pooled data from the first year of OctLAR therapy in all 40 individuals who received OctLAR (during their first year in the 26 O→O patients or second year in the 14 P→O patients), we detected a −6.08 ± 7.58% (P = 0.001) reduction in TLV (Table 3) compared to a growth rate of 0.90 ± 8.35% during the year of placebo treatment in the P→O group (n = 14).

Secondary outcomes

Kidney volumes. For the final analysis of TKV, we excluded individuals with ADPLD (n = 8) and renal transplant recipients (n = 4); therefore, 8 participants in the placebo group who crossed over to OctLAR in Year 2 and 19 enrollees in the original OctLAR group who continued OctLAR during second year were evaluated (Table 1 and Figure 2B).

The eight patients initially randomized to placebo (P→O) showed no significant change in TKV during treatment with OctLAR in Year 2 (Δ% +0.41 ± 9.45%, P = 0.90) compared to a significant increase of 8.61 ± 10.07% (P = 0.046) in Year 1. The group of 19 patients receiving OctLAR for 2 years in this clinical trial (O→O) showed an increase in TKV from 1152 ± 869 to 1214 ± 884 mL (or by 6.49 ± 7.08%, P = 0.0008) during the second year (Table 2).
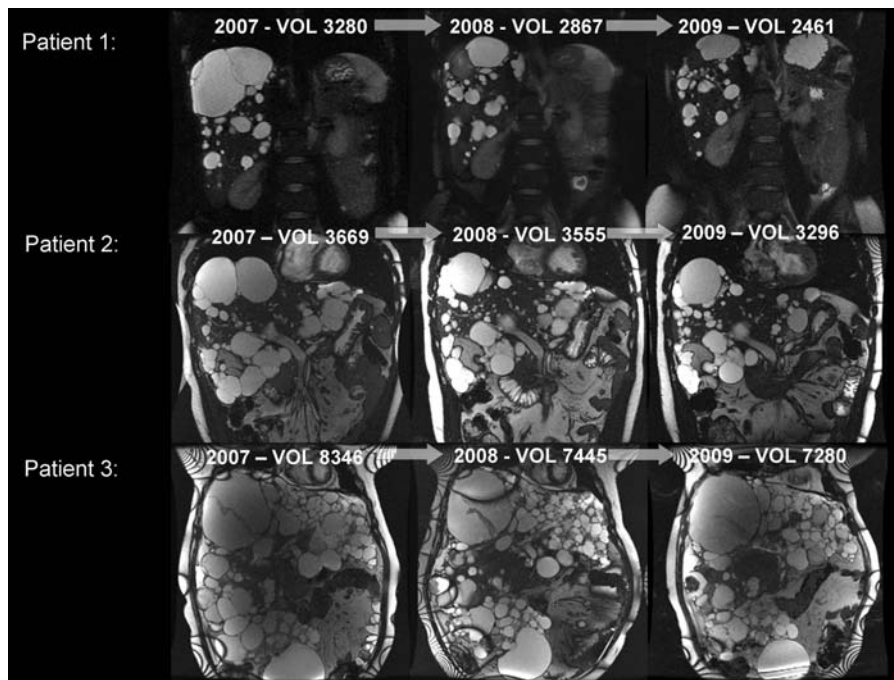
Fig. 3. Reduction of liver cyst burden in patients receiving continuous OctLAR therapy. Representative serial coronal abdominal and pelvic MRI views of three participants who underwent OctLAR therapy for 2 years. The images are standardized to visualize interval change in large cysts attributable to OctLAR therapy. Patient 1 had a decrease of 25%, Patient 2 of 10% and Patient 3 of 13% in TLV.

Table 2. Changes in liver and kidney volumes and renal function in subjects randomized to octreotide (O) for Year 1, all whom remained on octreotide for Year 2[a]

	Duration of treatment (year)			Change on O Δ Year 0, Year 1	Change on O Δ Year 1, Year 2
	0	1	2		
Total liver volume, cc					
N	26	26	26		
Mean (SD)	5984 (2961)	5628 (2720)	5649 (2870)	355.35 (471.24)	20.75 (440.52)
% Change				−5.23 (6.22)	−0.77 (6.82)
P-value				0.0002	0.57
TKV, cc w/o ADPLD					
N	19	19	19		
Mean (SD)	1152 (869)	1139 (838)	1214 (884)	−13.20 (74.87)	75.97 (124.46)
% Change				0.42 (7.61)	6.49 (7.08)
P-value				0.81	0.0008
GFR, mL/min/1.73BSA w/o ADPLD					
N	21	21	20		
Mean (SD)	68.1 (26.5)	64.6 (25.7)	57.7 (23.5)	−3.52 (10.53)	−5.65 (8.44)
% Change				−5.1 (15.5)	−7.9 (13.8)
P-value				0.15	0.019

[a]P-values for Year 2 versus Year 1 in liver volume, renal volume, GFR and creatinine (assessed as percent changes) are 0.0022, 0.013, 0.73 and 0.77, respectively. Paired *t*-test was used for statistical analysis within group. Using Wilcoxon signed rank test, the only change found to be significant was GFR while on OctLAR in the first year (0.045).

During the first year of OctLAR treatment in 27 patients who received one full year of OctLAR therapy (first year in the 19 O→O patients or second year in the 8 P→O patients), TKV increased by 0.42 ± 8.01% (P = 0.79) compared to a growth rate of 8.61 ± 10.07% during the year of placebo treatment in the P→O group (Tables 1 and 3). Thus, OctLAR therapy stalls kidney growth during the first year of treatment, but the effect does not appear to be sustained during Year 2.

Glomerular filtration rate. Changes in GFR (limited to ADPKD patients) in the placebo group (*n* = 9) in Year 1 (−7.2 ± 13.2% from baseline) and in Year 2 after crossing over to OctLAR (−6.3 ± 13% compared to Year 1) were not significantly different (Table 1). There were also no differences in the serum creatinine levels. In individuals who received OctLAR in their first year, GFR decreased by −5.1 ± 15.5% (*n* = 20, P = 0.15) and continued to decline (−7.9 ± 13.8%, P = 0.019) during the second year

Table 3. Pooled analysis of changes in liver and kidney volumes and renal function (GFR and creatinine) during 1 year of octreotide (O) therapy[a]

	Duration of treatment Δ Year 1 on OctLAR
Total liver volume, cc	
N	40
Mean (SD)	−373.92 (585.86)
% Change	−6.08 (7.58)
P-value	0.001
Total kidney volume, cc w/o ADPLD	
N	27
Mean (SD)	−5.86 (76.43)
% Change	0.42 (8.01)
P-value	0.79
GFR, mL/min/1.73BSA w/o ADPLD	
N	30
Mean (SD)	−3.4 (9.8)
% Change	−5.4 (14.5)
P-value	0.0501
Creatinine, mg/dL w/o ADPLD	
N	30
Mean (SD)	0.05 (0.14)
% Change	4.5 (12.5)
P-value	0.0597

[a]Pooled analysis was performed for all individuals who received OctLAR for 1 year (during either Year 1 in the O→O and Year 2 in the P→O group). Wilcoxon signed rank test revealed the same P-values for TLV and TKV, creatinine (0.0506) GFR (P = 0.02).

(Table 2). Pooled analysis of GFR in the 30 individuals who received 1 year of OctLAR revealed a decline of 5.4 ± 14.5% during the first year of treatment (P = 0.05) (Table 3).

Laboratory parameters. Prothrombin time was 9.6 (range 8.4–11.0) at baseline and at reassessment 10.6 (range 9.6–11.8) in individuals receiving OctLAR (P = 0.38) without any detectable clinical consequence. One patient taking warfarin was asked to hold the medication for 2 days prior to her monthly injection so as to avoid gluteal hematoma at the injection sites. There was a non-significant trend toward a reduction in aspartate transaminase (normal range 8–48 U/L) in the OctLAR group from Year 1 to Year 2 (32.5 U/L at baseline to 29.9 U/L by end of Year 1 and 27.1 U/L at completion of Year 2, P = 0.12). There were no significant differences in albumin, bilirubin or alkaline phosphatase, all of which remained within normal limits.

Fasting plasma glucose levels increased by 8% from baseline after commencing OctLAR treatment compared with a 2% increase in placebo group (P = 0.33) during the first year. No patient developed diabetes during the study. We did not observe any significant fluctuations in cyclosporin levels in the three renal transplant recipients receiving both medications throughout Year 2.

Tolerability. Repeated administration of OctLAR resulted in a low incidence of treatment-related adverse events. One individual was withdrawn from the study after Year 1 due to steatorrhea and weight loss, which were considered due to the medication. There were three serious adverse events in Year 2—one individual had chest pain, another developed an infected liver cyst(s) and

a third was hospitalized with urosepsis. None of these were considered to be due to the study medication. The target dose (40 mg) was reached in 35/41 (85%) patients. The dose was reduced to 30 mg in four (10%) and to 20 mg in two individuals (5%), mostly because of diarrhea/loose stools, especially in the first 2 weeks after an injection. As was seen in the first year, the most common adverse events observed in Year 2 were injection site pain or granuloma (n = 16/28, 57%) and diarrhea (n = 8, 28%).

After completing the study, one individual developed abdominal pain and underwent surgery for a presumptive diagnosis of acute cholecystitis (this occurred 1 month after completion of the study). A CT obtained immediately prior to her surgical procedure was used for her final TLV and TKV assessments. It was felt that the complication was not drug related, as the gallstone disease predated study enrollment. Another patient was hospitalized following a fall that was complicated by acute renal failure. This hospitalization was not considered to be related to the study medication.

Quality of life. For those individuals receiving continued OctLAR treatment for 2 years, statistically significant improvements of QOL in three subdomains were observed: (i) physical role (P = 0.0031), (ii) bodily pain (P = 0.0035) and (iii) vitality (P = 0.0022) compared with their baseline status (assessed at enrollment). While mean scores in the patients randomized to placebo did not significantly improve following 1 year of OctLAR treatment, non-significant trends towards improvement over 2 years were observed in seven of eight QOL subdomains although only one (general health perception) was close to significance (P = 0.056).

Discussion

Several studies have reported the substantial positive effects of somatostatin analogs in decreasing liver and kidney growth in PKD and ADPLD over a treatment period of 6 months. Our study extends information on the safety and efficacy of OctLAR in polycystic liver and kidney disease utilizing data from three patient groups: (i) 14 individuals with ADPKD and ADPLD who crossed over to OctLAR in their second year following 1 year of placebo (P→O), (ii) 26 patients who completed 2 years of continued OctLAR therapy (O→O) and (iii) a pooled analysis of a total of 40 patients who received at least 1 year of OctLAR therapy during the first year of treatment. In patients initially randomized to placebo and then crossed over to receive OctLAR (P→O), we observed even more substantial reductions in TLV (−7.66 ± 9.69%) compared to those seen in our original treated cohort (−4.95 ± 6.77%) [2]. Moreover, during the first year of active OctLAR treatment, TKV did not change (i.e. 0.42 ± 8.01%; Table 3) compared to the 8.61 ± 10.07% growth in the patients on placebo. These data suggest that OctLAR therapy may also have a beneficial effect on kidney growth at least for the initial first year of treatment. The principal finding of this study, however, is that continuous OctLAR therapy in the 26 patients with PLD

(O→O) sustained liver growth arrest over 2 years of treatment and that this treatment is relatively well-tolerated. From the pooled analyses of 40 patients who received 1 year of OctLAR therapy, we observed an overall 6.08% reduction in TLV. We will continue to follow these individuals for a further 2 years.

While OctLAR inhibited renal enlargement within the first year of treatment, it appeared to lose effectiveness during Year 2. Several reasons may account for the reduction of effect seen in Year 2. First, somatostatin receptors may undergo receptor downregulation/desensitization (probably by endocytosis of the receptor–ligand complexes) after prolonged exposure to OctLAR [14–16]. Second, we did not monitor OctLAR levels in plasma, its metabolism, cAMP concentration, or whether levels of the effectors IGF, GH or EGF were modulated by therapy. In the preclinical animal studies, liver and kidney effects were dose-dependent; therefore, higher doses of somatostatin analogs may be required [1]. Third, OctLAR is known to bind to three of five known somatostatin receptors (SSTRs)—SSTR2, SSTR3 and SSTR5. At this point, we do not know what SSTRs are present in liver and kidneys of our patients, and how their expression is different from normal hepatic and renal epithelia. Thus, the use of more potent somatostatin analogs binding to a broader range of SSTRs might be more efficient. Alternatively, their use in combination with other anti-proliferative and anti-secretory agents, e.g. low-dose mammalian target of rapamycin mTOR inhibitors (a pathway known to be implicated in the pathogenesis of progressive liver and kidney enlargement in PKD), may be another feasible strategy and the combination of octreotide and everolimus is currently being evaluated in the extended low-intensity anticoagulation for thromboembolism trial for PLD (NCT01157858) [17].

While the results of OctLAR therapy on TLV are clearly positive and results on TKV may show some benefit, we did not detect any positive effect of OctLAR on GFR. Possible reasons for this may be (i) the increase in TKV was not inhibited during Year 2 of OctLAR treatment, (ii) the small number of patients evaluated for this secondary outcome (21 O→O and 9 P→O patients), (iii) the relatively short duration of the study, (iv) somatostatin-induced renal vasoconstriction causing a reduction in renal blood flow and GFR [18] and most importantly, (v) the non-linearity of GFR decline in ADPKD. For example in the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) longitudinal study of 241 patients with normal GFR at entry, GFR remained stable from baseline to Year 3 but decreased markedly at Year 6 and Year 8 pointing to a phase of accelerated rate of GFR decline after many years of GFR stability [19]. Of the 30 ADPKD patients in our study, 12 had established chronic kidney disease 3 (CKD3) and 1 had CKD4 at enrollment. Given these limitations, larger placebo-controlled studies of longer duration will be necessary to determine the effect of somatostatin analogs on the progression of CKD in ADPKD.

As our primary study end point focused on TLV, we selected ADPLD and ADPKD patients with severely enlarged livers. Therefore, the patients in this study represent a minority of PLD patients with more severe liver disease than the 'average' ADPKD patient and we restrict the use of somatostatin analogs to this patient subgroup (i.e. >4000 mL liver volume with symptomatic PLD).

Potential limitations of this study include missing imaging in one patient and reliance on CT instead of MRI for image acquisition in four individuals. Despite finding an excellent correlation between these two different imaging techniques, they could result in a potential source of measurement bias. Thus, we used the same image acquisition technique at each patient visit to minimize the potential for measurement error. Average intra-observer and inter-observer variability are 1.12 and 3.2%, respectively. Variability was similar regardless of whether CT or MRI was used.

The majority of individuals tolerated the 40 mg OctLAR dose. Only one individual was discontinued from the study after 12 months because of drug-related side effects (steatorrhea, despite initiation on pancreatic enzyme supplements)—all the other 41 individuals receiving OctLAR had an acceptable side effect profile. One individual with Stage 4 CKD and another with Stage 3 CKD needed reduction in dose to 30 mg. Dose adjustments are advised for patients with severe renal impairment. Cases of hyperkalemia (due to the drug's impact on insulin-mediated potassium transport) have been reported in patients on dialysis [20–22]. Therefore, the starting dose for patients on dialysis should not exceed 10 mg every 4 weeks according to the product information sheet for Sandostatin LAR (octreotide). We restricted the trial to patients with creatinine <3 mg/dL for safety considerations. The most common adverse events were injection site pain and granuloma, although no participant discontinued therapy for that reason. Patients undergoing long-term OctLAR treatment should be monitored for cholelithiasis symptoms or signs, since this is a known complication [23–26]. Prothrombin time should be monitored before surgical procedures while patients are receiving OctLAR.

It is our opinion that a 6% reduction in massive PLD is clinically significant in terms of patient comfort and this is supported by the persistent improvement in QOL in the patients treated with octreotide for 2 years and possibly by a non-significant trend in the smaller group of placebo-treated patients switched to octreotide treatment during the second year. We continue to use this medication in patients with highly symptomatic PLD and severe hepatomegaly who are not candidates for or wish to avoid or delay (the majority being women engaged in home and family life or mid-career) surgical management. Furthermore, most patients chose to continue the therapy after their second year in an open-label extension and have averted or delayed surgical management. More precise definition of the role of somatostatin analogs and the optimal timing for initiation of therapy will require studies of longer duration in a larger number of patients.

In conclusion, while this is a small study, it further substantiates the positive effects of somatostatin analogs in reducing TLV, demonstrating they are safe and efficacious over a 2-year period in individuals with ADPKD or ADPLD, many of whom had chronic renal insufficiency. It remains to be seen if more potent somatostatin analogs

or the combination of somatostatin analog with other growth inhibitor pharmacotherapies will be more effective in the medical management of this disease.

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