Reducing Polycystic Liver Volume in ADPKD: Effects of Somatostatin Analogue Octreotide

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Background and objectives: No medical treatment is available for polycystic liver disease, a frequent manifestation of autosomal-dominant polycystic kidney disease (ADPKD). In a prospective, randomized, double-blind, crossover study, 6 months of octreotide (40 mg every 28 days) therapy limited kidney volume growth more effectively than placebo in 12 patients with ADPKD.

Design, setting, participants, & measurements: In this secondary, *post hoc* analysis of the above study, octreotide-induced changes in liver volumes compared with placebo and the relationship between concomitant changes in liver and kidney volumes were evaluated. Those analyzing liver and kidney volumes were blinded to treatment.

Results: Liver volumes significantly decreased from 1595 ± 478 ml to 1524 ± 453 ml with octreotide whereas they did not appreciably change with placebo. Changes in liver volumes were significantly different between the two treatment periods (−71 ± 57 ml *versus* +14 ± 85 ml). Octreotide-induced liver volume reduction was fully explained by a reduction in parenchyma volume from 1506 ± 431 ml to 1432 ± 403 ml. Changes in liver volumes were significantly correlated with concomitant changes in kidney volumes ($r = 0.67$) during octreotide but not during placebo treatment. Liver and kidney volume changes significantly differed with both treatments (octreotide: −71 ± 57 ml *versus* +71 ± 107; placebo: +14 ± 85 ml *versus* +162 ± 114), but net reductions in liver (−85 ± 103 ml) and kidney (−91 ± 125 ml) volume growth on octreotide *versus* placebo were similar.

Conclusions: Octreotide therapy reduces liver volumes in patients with ADPKD and is safe.

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Polycystic liver disease is the most frequent extrarenal manifestation of autosomal-dominant polycystic kidney disease (ADPKD) but may occur also as an isolated clinical entity (1). Prevalence in ADPKD increases with age and approximates 95% by the age of 35 years (2). Symptoms worsen with time in parallel with progressive and massive enlargement of the liver and may be particularly severe in older patients who have survived long enough to progress to end-stage kidney disease and need for renal replacement therapy (1). Progressively enlarging livers compress gastrointestinal tract, inferior cava vein and portal vein, or bile ducts and may cause low-back pain, early satiety, gastroesophageal reflux, and obstruction of venous and biliary outflow and secondary ascites or jaundice. Abdominal distension may cause incapacitating dyspnea. Cysts may also rupture, bleed, or become infected. So far, only invasive procedures are available to ameliorate disease symptoms including cyst aspiration or fenestration to limit compression on surrounding structures and drainage of the ascitic fluid to reduce abdominal distension. Liver resection or transplantation may be needed in most severe cases (1).

Hepatic cysts derive from cholangiocytes that proliferate and secrete fluid in response to endogenously activated cAMP (3). Cholangiocytes express somatostatin receptors, and cholangiocyte exposure to somatostatin reduces cellular cAMP levels and cell proliferation and secretion *in vitro* (4). The somatostatin analogue octreotide significantly reduced liver weight and mitotic indices in rats with polycystic disease, an effect associated with a reduction in cholangiocyte and serum cAMP levels (4). These data provided the rationale for assessing the role of octreotide in the treatment of polycystic liver in humans (5).

A prospective, randomized, crossover, double-blind, placebo-controlled study showed that 6 months of octreotide therapy limited kidney volume growth *versus* placebo in 12 patients with ADPKD (6) possibly through inhibition of cAMP production and activity (7). To assess the treatment effect on polycystic liver, in this *post hoc* analysis of the above study we primarily compared liver volume changes during octreotide and placebo therapy in the same population. Secondarily, we evaluated the

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relationships between liver and kidney volume changes during both treatment periods. Data are reported conforming to Consolidated Standards of Reporting Trials guidelines (8).

Materials and Methods

Patients

Pedigrees of patients were analyzed for linkage to polycystic kidney disease 1 (*PKD1*) or 2 (*PKD2*) genes with microsatellite markers (9). The markers D16S521 and D16S291 were used for *PKD1* and the markers D4S1534 and D4S423 were used for *PKD2* linkage analyses, respectively. Haplotypes were reconstructed using the Genehunter package (version 1.2). Adults with a serum creatinine concentration <3 mg/dl, but >1.2 mg/dl (men) or >1.0 mg/dl (women), and without biliary or urinary tract lithiasis at screening ultrasound evaluation were eligible for study participation (6). Those with concomitant liver or renal parenchymal disease different from polycystic disease; more than two hemorrhagic or complicated cysts; biliary or urinary tract obstruction or infection; urinary protein excretion rate >1 g/24 h or abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease; diabetes, cancer, or major systemic diseases that could prevent completion of the planned follow-up or interfere with data collection or interpretation; psychiatric disorders or any condition that could prevent full comprehension of the purposes and risks of the study; and pregnant or lactating women or fertile women without effective contraception were not considered eligible for study participation.

Study Design

This was a *post hoc* analysis of a prospective, randomized, crossover, double-blind, placebo-controlled trial designed, conducted, and monitored by the Investigators of the Clinical Research Center for Rare Diseases "Aldo & Cele Daccò" of the Mario Negri Institute for Pharmacologic Research in cooperation with the Units of Nephrology and Radiology of the Azienda Ospedaliera "Ospedali Riuniti of Bergamo." The ethical committees of both institutions approved the study protocol, and eligible patients provided written informed consent to study participation according to the Declaration of Helsinki guidelines. The trial was not registered because patient inclusion and treatment was completed in 2002 when there were no indications to trial registration yet.

Baseline Evaluations. At baseline evaluation, the mean of three blood pressure (BP) measurements was recorded for statistical analyses. Biologic samples were taken in the morning with the patient fasting from the evening before for routine laboratory evaluations; these included routine hematochemistry, renal and liver function tests, and coagulation tests. Total liver and kidney volumes, liver cyst and parenchymal volumes, and kidney cyst and parenchymal volumes were evaluated by spiral computerized tomography (CT) and morphometric analyses. The GFR was measured by the iohexol plasma clearance technique (10).

Stratification and Randomization. After baseline evaluation, eligible patients were stratified by presence or absence of macroscopic liver cysts and randomly assigned to the treatment sequence somatostatin-placebo or placebo-somatostatin in blocks of four using a 1:1 allocation ratio. The Laboratory of Biostatistics of the Clinical Research Center centrally randomized patients according to a computer-generated randomization list. Doctors and nurses in charge of patient treatment and monitoring, radiologists (M.C., G.F.) and computer scientists (A.C., L.A., A.R.) involved in CT scan image acquisition and evaluations, and technicians performing the laboratory analyses were all blinded to treatment allocation.

Treatment and Follow-Up. Participants were allocated to start a 6-month treatment period with the long-acting somatostatin analogue octreotide-LAR (Sandostatin LAR Depot: Novartis Pharma AG, Basel, Switzerland) or placebo (saline with an identical image), which were both administered by two 20-mg intragluteal injections every 28 days. Active drug or placebo were prepared and administered by a nurse that was not involved in patient care and data recording or analysis. BP, routine laboratory tests, and liver and kidney ultrasonographic appearance were evaluated every 2 months. At 6 months, all of the measurements performed at baseline evaluation (including CT and GFR evaluations) were repeated, and each patient crossed over to the other treatment arm. The same measurements performed during the first treatment period were repeated every 2 months, and at completion of the second treatment period all baseline evaluations were repeated before patients were discharged from the study.

Co-Interventions. No systematic change in diet and pharmacologic treatment was introduced throughout the study period unless deemed clinically appropriate to control BP or limit the signs of liver or renal dysfunction. Any change in concomitant treatments was reported and justified in patients' case record forms.

Spiral CT Scanning and Volumetric Analyses

Volumes of liver and kidney structures were evaluated by a two-slice CT scanner (CT-Twin; Elscint, Haifa, Israel). Single breath-hold CT acquisitions were started 90 seconds after start of an intravenous injection of 170 ml of nonionic contrast agent (Iopamiro, Bracco, Milano,

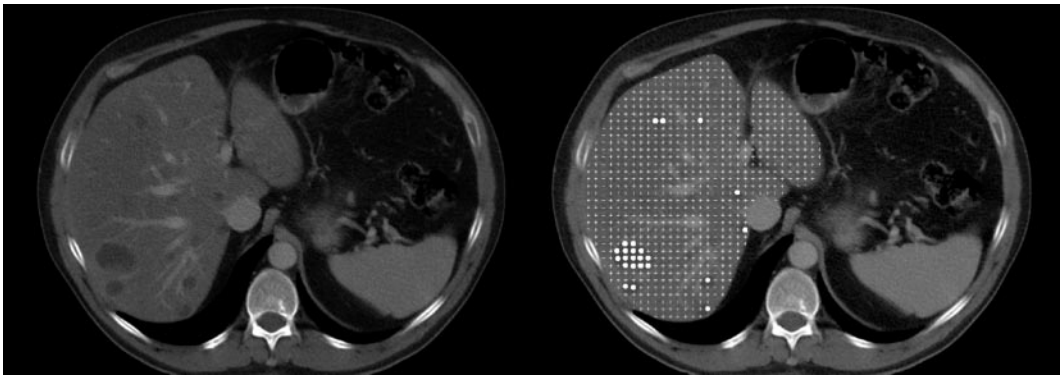

Figure 1. Volume quantification method using stereology. Original CT image of a baseline liver scan acquisition from patient 3 (left), and the same liver scan with a stereology grid showing points within the liver parenchyma (crosses) and within cysts (full circles).

Italy) at a rate of 2.5 ml/s. The same scanning parameters (voltage 120 kV, current 230 mA, field-of-view 43 cm, matrix 512 × 512, collimation 5 mm, pitch 1, increment 3 mm, and overlap >50%) were adopted for all acquisitions. After acquisition, images were directly transferred to a workstation in DICOM format and used for digital morphometry.

Total liver and liver cyst volumes were quantified at each time point by a validated stereology method (11). For each patient, a regular grid with 1-cm point spacing was randomly superimposed to every CT image using a general purpose image processing software (ImageJ, http://rsbweb.nih.gov/ij/), and the number of intersections with the whole liver and with cysts were counted (Figure 1). Total liver volume and cyst volume were then obtained by multiplying the intersection count by the grid point area times the slice thickness ($1 \times 1 \times 3$ cm^3). Total kidney and kidney cyst volumes were computed as previously described and validated (6,12).

Statistical Analyses

Significance of differences in total liver volume changes between octreotide and placebo treatment and in total liver *versus* total kidney volume changes was assessed by a nonparametric Wilcoxon test for paired observations, whereas the relationships between concomitant changes in total liver and kidney volumes were evaluated by nonparametric Spearman's rank correlation. Statistical analyses were carried out using the R statistical software (http://www.r-project.org).

Results

Patients

Fourteen patients entered the study. On the basis of history and linkage analysis, nine patients were diagnosed with the *PKD1* and one with the *PKD2* form. In four subjects, the differential diagnosis between *PKD1* and *PKD2* was uncertain. Two patients were withdrawn 3 and 5 months after inclusion, respectively: the first one reported asthenia and the second one was found at routine ultrasound evaluation to have two nonsymptomatic small gallstones that were not present at inclusion and dissolved after 2 months of treatment with ursodeoxycholate acid. When the database was locked and the randomization code opened, the two subjects were found to be on placebo and octreotide, respectively. The remaining 12 patients (nine men and three women, ages 35 to 58 years, median 44.5 years) completed the study.

Table 1. Liver and kidney structural parameters before and after 6 months of treatment with octreotide or placebo according to treatment sequence and in the study group as a whole[a]

Parameter	Baseline	Placebo		Octreotide	
		Before	After	Before	After
Octreotide first ($n = 5$)					
liver volumes					
total, ml	–	1375 ± 186	1440 ± 188	1443 ± 170	1375 ± 186
cyst, ml	–	32 ± 38	32 ± 41	30 ± 38	32 ± 38
parenchyma, ml	–	1343 ± 201	1400 ± 188	1413 ± 192	1343 ± 201
kidney volumes					
total, ml	–	1877 ± 339	1987 ± 409	1816 ± 242	1877 ± 339
cyst, ml	–	1176 ± 303	1243 ± 343	1115 ± 265	1176 ± 303
parenchyma, ml	–	220 ± 64	233 ± 78	222 ± 60	220 ± 64
Placebo first ($n = 7$)					
liver volumes					
total, ml	–	1726 ± 593	1704 ± 605	1704 ± 605	1631 ± 567
cyst, ml	–	131 ± 186	131 ± 182	131 ± 182	136 ± 196
parenchyma, ml	–	1596 ± 543	1573 ± 551	1573 ± 551	1495 ± 509
kidney volumes					
total, ml	–	2878 ± 1060	3076 ± 1106[c]	3076 ± 1106	3155 ± 1181
cyst, ml	–	1999 ± 928	2134 ± 980[c]	2134 ± 980	2194 ± 1029
parenchyma, ml	–	257 ± 61	264 ± 70	264 ± 70	249 ± 68
Whole sample ($n = 12$)					
liver volumes					
total, ml	1608 ± 473	1580 ± 487	1594 ± 480	1595 ± 478	1524 ± 453[b]
cyst, ml	89 ± 149	89 ± 148	89 ± 146	89 ± 146	93 ± 156
parenchyma, ml	1519 ± 428	1490 ± 439	1504 ± 433	1506 ± 431	1432 ± 403[b]
kidney volumes					
total, ml	2435 ± 966	2461 ± 959	2623 ± 1021[b]	2551 ± 1053	2622 ± 1111[c]
cyst, ml	1631 ± 838	1656 ± 826	1762 ± 882[b]	1709 ± 908	1770 ± 941
parenchyma, ml	242 ± 61	242 ± 62	251 ± 72	247 ± 67	237 ± 65

[a]Baseline data in the whole cohort are independent of treatment sequence, and data are presented as mean ± SD.
[b]$P < 0.005$ *versus* start at Wilcoxon test for paired observations.
[c]$P < 0.05$ *versus* start at Wilcoxon test for paired observations.

Table 2. Individual liver volumes (ml) before and after 6 months of treatment with placebo or octreotide

Patient Number[a]	Total Liver Volume				Total Cyst Volume				Parenchyma Volume			
	Placebo		Octreotide		Placebo		Octreotide		Placebo		Octreotide	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	1179	1214	1214	1159	0	0	0	0	1179	1214	1214	1159
2	2212	2190	2190	2037	336	297	297	307	1876	1893	1893	1730
3	2788	2809	2809	2660	114	139	139	125	2675	2669	2669	2535
4	1109	1090	1090	1047	0	0	0	0	1109	1090	1090	1047
5	1537	1396	1396	1314	8	10	10	11	1529	1386	1386	1303
6	1712	1682	1682	1735	449	458	458	501	1263	1225	1225	1234
7	1546	1544	1544	1467	8	10	10	10	1538	1534	1534	1457
8	1578	1599	1670	1578	0	0	0	0	1578	1559	1670	1578
9	1506	1512	1513	1506	63	51	52	63	1443	1460	1461	1443
10	1201	1407	1279	1201	81	94	86	81	1120	1312	1193	1120
11	1431	1554	1486	1431	0	0	0	0	1431	1554	1486	1431
12	1159	1128	1268	1159	14	13	12	14	1145	1115	1256	1145

[a]Patients 1 to 7: first treatment period = placebo; patients 8 to 12: first treatment period = octreotide.

Clinical Characteristics. Main patient characteristics at inclusion have been reported in detail (6). Briefly, systolic and diastolic BP averaged 144 ± 12 mmHg and 94 ± 12 mmHg, respectively. Serum aspartate aminotransferase levels were in normal ranges in all patients, and alanine aminotransferases and gamma glutaryl transaminases levels exceeded the upper limit of the normal range in one and three patients, respectively. In no instances did the levels exceed the double of the upper limit. Alkaline phosphatase and biliary acid levels exceeded the upper limit of the normal range in two patients. Median (range) GFR was 57.1 (24.4 to 95.3) ml/min/1.73 m^2.

Liver and Kidney Volumes. At inclusion, all patients showed enlarged livers and eight patients had macroscopic liver cysts (Table 1). The increase in total liver volumes was mostly explained by increased parenchyma volumes, which exceeded the "normal" volumes (13) by approximately 30%. Total kidney volumes were larger than total liver volumes mostly because of the volumes of the kidney cysts that largely exceeded the volumes of the liver cysts (Table 1). No patient had hemorrhagic or complicated cysts.

Outcomes

Safety. As previously reported (6), treatment was well tolerated in all patients. During both treatment periods there were no changes in clinical or laboratory parameters (including liver transaminases) considered by the investigators to have any

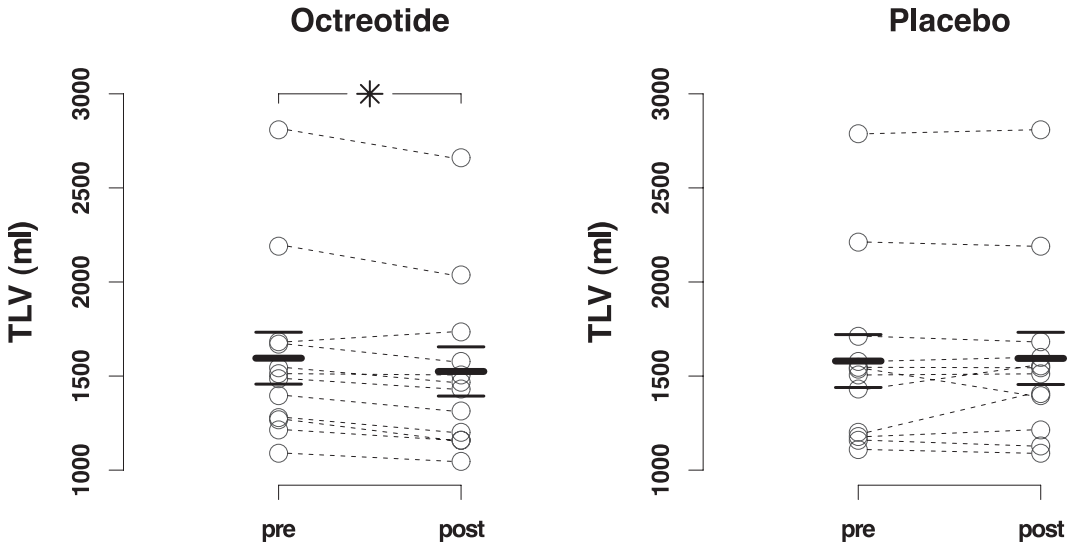

Figure 2. Absolute changes in total liver volume (delta TLV) during 6 months of octreotide or placebo therapy in 12 patients with ADPKD. Horizontal thick and thin segments denote mean and SEM, respectively. *$P < 0.005$ *versus* pretreatment TLV (Wilcoxon test for paired observations).

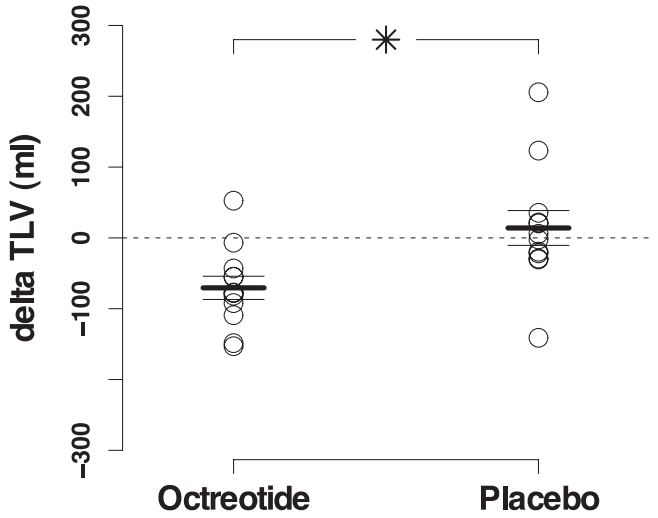

Figure 3. Absolute changes in total liver volume (delta TLV) during 6 months of octreotide or placebo therapy in 12 patients with ADPKD. Horizontal thick and thin segments denote mean and SEM, respectively. *$P < 0.05$ octreotide *versus* placebo (Wilcoxon test for paired observations).

clinical relevance. In no patient did the dosage of octreotide or placebo have to be reduced or treatment interrupted because of adverse events.

Efficacy. Average changes in liver and kidney volume for the overall population and according to treatment sequence are reported in Table 1, whereas individual changes are detailed in Table 2. Total liver volume significantly decreased during octreotide therapy but did not change appreciably during placebo (Table 1 and Figure 2). Thus, changes in liver volumes during octreotide and placebo therapy were significantly different (-71 ± 57 ml *versus* $+14 \pm 85$ ml, respectively, $P < 0.05$, Figure 3). Octreotide-induced reduction in total liver volume ($P < 0.005$) was fully explained by a significant reduction in parenchyma volume from 1506 ± 431 ml to 1432 ± 403 ml ($P < 0.005$) with no appreciable changes in liver cyst volume (Table 1). No significant change in liver parenchyma or cyst volume was observed on placebo (Table 1). Similar trends during the two treatment periods were observed in the five patients who received octreotide before placebo and in the seven patients randomized to the opposite treatment sequence.

Total kidney volume significantly increased during octreotide and placebo (Table 1), but increases in total kidney volume during octreotide were significantly lower than those observed during placebo (162 ± 114 ml *versus* 71 ± 107 ml, $P < 0.05$). Kidney cyst volume significantly increased by 61 ± 106 ml during placebo but did not appreciably change during octreotide (Table 1).

Within-patient absolute changes in total liver and kidney volumes were significantly correlated during octreotide treatment ($r = 0.67$, $P < 0.05$) but not during placebo ($r = 0.21$, $P = 0.51$, Figure 4). Changes in liver and kidney volumes were significantly different during octreotide therapy (-71 ± 57 ml *versus* $+71 \pm 107$ ml, $P < 0.0005$) and during placebo ($+14 \pm 85$ ml *versus* $+162 \pm 114$, $P < 0.005$; Figure 5), but net reductions in volume growth for liver (-85 ± 103 ml) and kidney (-91 ± 125 ml) achieved by octreotide compared with placebo were similar ($P = 0.79$).

Discussion

In these *post hoc* analyses of a prospective, randomized, double-blind, crossover, placebo-controlled study primarily aimed at assessing the effects of the long-acting somatostatin analogue octreotide in 12 ADPKD patients with polycystic livers, we observed a significant reduction in total liver volume during 6 months of active treatment, whereas no appreciable change was observed during placebo. Consequently, changes in liver volumes were significantly different between the two treatment periods. Of note, changes in total liver volumes on octreotide strongly correlated with concomitant changes in total kidney volumes. Evidence that this correlation was observed during octreotide therapy, but not during placebo, corroborates the hypothesis that octreotide-associated changes in liver and kid-

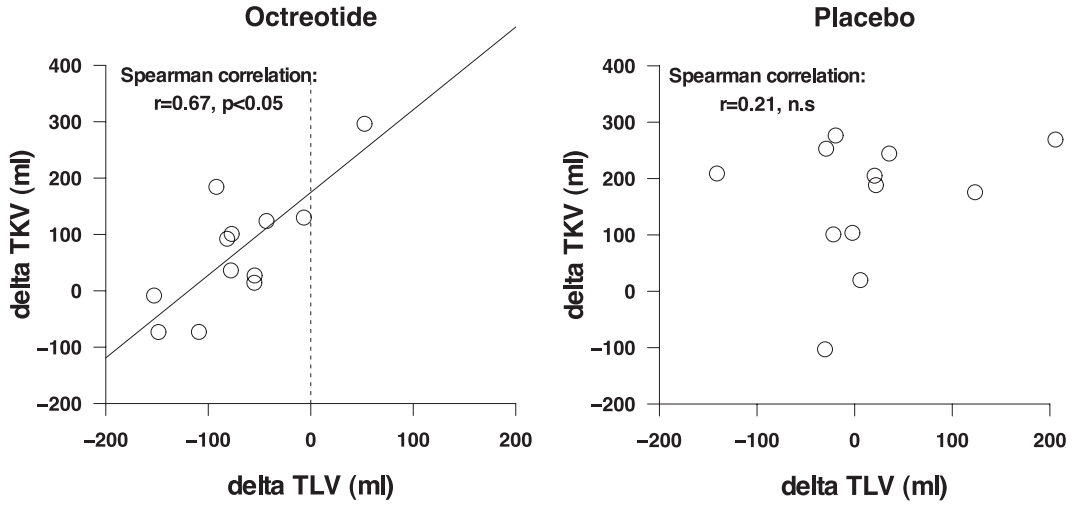

Figure 4. Correlations between absolute changes in total liver volumes (delta TLV) and concomitant changes in total kidney volumes (delta TKV) during 6 months of (left) octreotide or (right) placebo therapy (Spearman correlation).

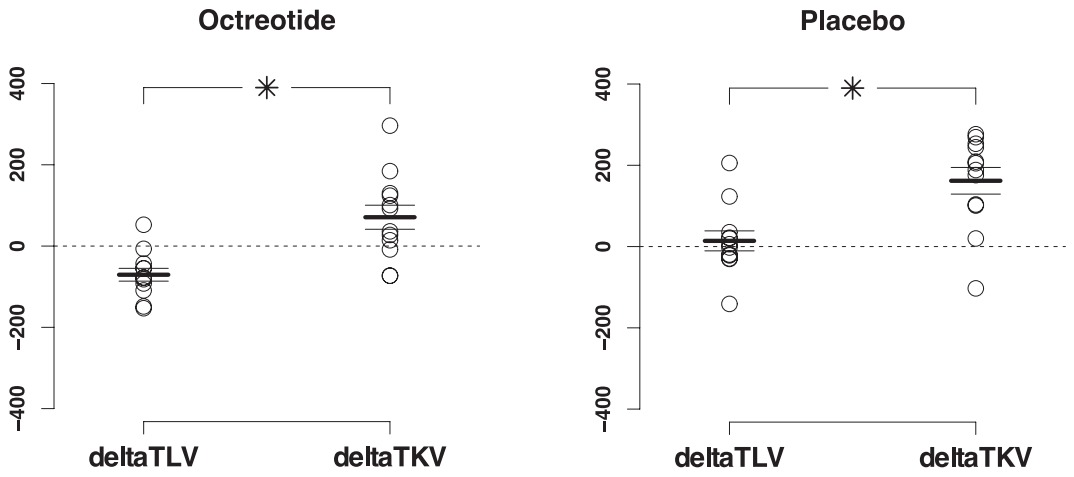

Figure 5. Changes in total liver volume (delta TLV) and total kidney volume (delta TKV) during 6 months of (left) octreotide or (right) placebo therapy. *$P < 0.0005$ and $P < 0.005$ between delta TLV and delta TKV during octreotide and placebo treatment, respectively (Wilcoxon test for paired observations).

ney volumes reflected a specific treatment effect rather than the natural history of the disease. Treatment was also well tolerated and was not associated with any clinically relevant change in any considered safety parameter. Indeed, only two patients prematurely withdrew from the trial because of asthenia reported after 3 months of placebo treatment in one case and detection of two nonsymptomatic gallstones at per-protocol ultrasound evaluation after 5 months of treatment with octreotide in the second case. Notably, this adverse event fully recovered with the dissolution of the gallstones over 2 months of treatment with ursodeoxycholate acid.

Two patients with ADPKD and liver cysts were previously reported to have reduction in liver volumes during 4 and 8 months of octreotide therapy, respectively (14); however, data were uncontrolled and, most important, were confounded by concomitant treatments such as cyst aspiration or fenestration/ablation, which conceivably contributed to the reduction in liver volumes. Another clinical trial run in parallel with and independent of the study presented here found that a treatment period of the same duration (6 months) with another long-acting somatostatin analogue (lanreotide) achieved a reduction of liver volume in patients with autosomal-dominant polycystic liver disease or ADPKD (15) similar to the reduction we observed in ADPKD patients. Finding that lanreotide also limited the growth of kidney volumes in the subgroup of patients with ADPKD confirmed and extended our previous data that the growth of ADPKD kidneys can be prevented by octreotide therapy (6).

Of interest, in the study presented here octreotide-induced reduction in total liver volume was explained by the concomitant reduction in parenchyma volume without appreciable changes in macroscopic cyst volumes. We speculate that apparently normal parenchymal volume might include overgrown bile ductules and cysts with volumes smaller than the detection threshold of the CT scan evaluation (6), and that the reduction of these volumes might explain the reduction in the parenchymal volume we observed during octreotide treatment. This is consistent with *in vitro* evidence that octreotide-inhibited proliferation of cholangiocytes from rats with polycystic liver disease reduced the circumferential area of bile ducts and of new cysts even before the development of macroscopic cysts (4). However, larger studies are needed to confirm or reject the hypothesis that octreotide might reduce liver parenchyma volume because of its effects on smaller cysts.

On the other hand, lanreotide slowed the growth of livers (15) that on average were 2- to 3-fold larger than in our patients. Finding that treatment effect was similar in the two studies suggests that somatostatin analogues may limit liver growth independent of the stage of the disease. Unfortunately, the study by Keimpema and coworkers (15) did not report data on liver parenchyma and cyst volumes considered separately; thus, it is impossible to establish whether at later stages of the disease liver volume reduction is also explained by a reduction of apparently healthy parenchyma more (or rather) than of macroscopic cysts.

An additional finding of the study presented here was that liver compared with kidney volumes were less enlarged at inclusion and increased less during both treatment periods. This is consistent with previous evidence that in ADPKD patients the liver is generally less severely involved than the kidney, and liver disease progression results in organ failure less frequently than renal disease progression (1). Of note, the increase in liver volumes observed during placebo averaged 14 ml and treatment effect resulted in a significant volume reduction of 71 ml during octreotide administration. Conversely, the increase in kidney volume approximated 162 ml during placebo and was limited to 71 ml on octreotide. Thus, the reduction in volume growth observed during octreotide therapy compared with placebo was remarkably similar in the two organs (85 *versus* 91 ml, respectively). These findings are consistent with previous evidence that octreotide was similarly effective in preventing liver and kidney growth in rats with polycystic disease as well as in inhibiting biliary and tubular cell proliferation *in vitro* (4).

Safety

The remarkably good safety profile in the series presented here and in other clinical settings (16) suggests that octreotide could

also be a valuable option for chronic therapy of ADPKD patients. However, octreotide is not licensed for this indication and its use cannot be recommended before the risk/benefit profile of octreotide for chronic treatment of ADPKD is evaluated in adequately powered trials, in particular in patients with severe liver and kidney involvement. Finally, we remind readers that dose adjustments are advised for patients with severe renal impairment and that, according to the product information sheet for Sandostatin Lar (octreotide) Depot suspension injection, for patients on dialysis the starting dose should not exceed 10 mg every 4 weeks.

Limitations

The findings presented here must be taken with caution because of the small sample size and the relatively short follow-up. Moreover, they were generated from secondary analyses of a study primarily aimed at evaluating the effect of treatment on total kidney volume (6). However, these analyses were *post hoc*, and outcome variables under consideration here were measured and recorded as accurately as the primary outcome variable according to similar protocol guidelines. Moreover, standardized CT scan evaluations to limit random data fluctuations and intrapatients comparisons in the setting of a crossover design contributed to increasing the power of the analyses and, consequently, the reliability of the results. Finding that treatment effect was independent of treatment sequence reasonably excluded any appreciable carry-over effect. Finally, data robustness was confirmed by the consistency of the effects we observed on liver and kidney volumes.

In conclusion, in patients with ADPKD and nonsymptomatic liver involvement, 6 months of treatment with the long-acting somatostatin analogue octreotide reduced the growth of liver and kidney volumes and was well tolerated. These findings provide the rationale for adequately powered trials aimed to assess whether and to which extent octreotide therapy may improve clinical outcomes of ADPKD patients in the long run.

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Disclosures

None.

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