Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial

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Summary

Background **Autosomal dominant polycystic kidney disease slowly progresses to end-stage renal disease and has no effective therapy. A pilot study suggested that the somatostatin analogue octreotide longacting release (LAR) could be nephroprotective in this context. We aimed to assess the effect of 3 years of octreotide-LAR treatment on kidney and cyst growth and renal function decline in participants with this disorder.**

Methods **We did an academic, multicentre, randomised, single-blind, placebo-controlled, parallel-group trial in five hospitals in Italy. Adult (>18 years) patients with estimated glomerular filtration rate (GFR) of 40 mL/min per 1·73 m² or higher were randomly assigned (central allocation by phone with a computerised list, 1:1 ratio, stratified by centre, block size four and eight) to 3 year treatment with two 20 mg intramuscular injections of octreotide-LAR (n=40) or 0·9% sodium chloride solution (n=39) every 28 days. Study physicians and nurses were aware of the allocated group; participants and outcome assessors were masked to allocation. The primary endpoint was change in total kidney volume (TKV), measured by MRI, at 1 year and 3 year follow-up. Analyses were by modified intention to treat. This study is registered with ClinicalTrials.gov, NCT00309283.**

Findings **Recruitment was between April 27, 2006, and May 12, 2008. 38 patients in the octreotide-LAR group and 37 patients in the placebo group had evaluable MRI scans at 1 year follow-up, at this timepoint, mean TKV increased significantly less in the octreotide-LAR group (46·2 mL, SE 18·2) compared with the placebo group (143·7 mL, 26·0; p=0·032). 35 patients in each group had evaluable MRI scans at 3 year follow-up, at this timepoint, mean TKV increase in the octreotide-LAR group (220·1 mL, 49·1) was numerically smaller than in the placebo group (454·3 mL, 80·8), but the difference was not significant (p=0·25). 37 (92·5%) participants in the octreotide-LAR group and 32 (82·1%) in the placebo group had at least one adverse event (p=0·16). Participants with serious adverse events were similarly distributed in the two treatment groups. However, four cases of cholelithiasis or acute cholecystitis occurred in the octreotide-LAR group and were probably treatment-related.**

Interpretation **These findings provide the background for large randomised controlled trials to test the protective effect of somatostatin analogues against renal function loss and progression to end-stage kidney disease.**

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Introduction

Autosomal dominant polycystic kidney disease is the most common monogenic renal disorder, accounting for 8–10% of patients receiving renal replacement therapy for end-stage renal disease worldwide.[1] Its clinical phenotype is progressive and substantial enlargement of the kidneys, caused by sustained expansion of many fluid-filled cysts that originate from the tubule wall, leading to crowding of adjacent nephrons, injury to normal parenchyma,[2,3] and eventually kidney failure. No proven treatments exist and an effective disease-modifying drug would have important implications for patients.

The progressive enlargement of cysts derived from renal tubules is believed to be largely attributable to proliferation of mural epithelial cells and transport of fluid into cavities generated by accelerated epithelial cell growth.[4] In-vitro evidence suggests that this cell growth and transepithelial secretion of fluid is controlled by cyclic AMP (cAMP).[4] Somatostatin—a cyclic 14 aminoacid peptide secreted by pancreatic islets, the gastrointestinal tract, nervous system, and thyroid gland—is thought to inhibit adenyl cyclase and post-cAMP events in addition to fluid secretion stimulated by agents that do not generate cAMP.[5] These findings and the presence of specific receptors for somatostatin in human kidneys[6] led us to do a pilot feasibility study[7] with the somatostatin analogue octreotide longacting release (LAR) in 12 participants with autosomal dominant polycystic kidney disease with different degrees of renal insufficiency. The intention was to inhibit cAMP production in renal cells, thereby reducing rates of cell proliferation and fluid secretion.[7] 6 month octreotide-LAR treatment retarded by more than 60% the time-dependent increase in total kidney volume (TKV), compared with placebo in

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the same participants,[7] and reduced liver volumes in the same participants with concomitant polycystic liver disease.[8] Limitations of this study included the small number of participants, non-contemporary controls, and short follow-up. Octreotide-LAR also reduced cAMP in kidney and bile ducts and slowed progression of hepatorenal cystogenesis in rats with recessive polycystic kidney and liver disease.[9]

In view of the good safety profile of prolonged, even lifelong, octreotide-LAR treatment[10] and the encouraging results of our pilot trial,[7] we designed the effect of A Long-Acting somatostatin on DIsease progression in Nephropathy due to autosomal dominant polycystic kidney disease (ALADIN) trial, which aimed to assess the effect of 3 years of octreotide-LAR treatment on kidney and cyst growth and renal function decline in participants with autosomal dominant polycystic kidney disease with normal renal function or mild-to-moderate renal insufficiency.

Methods

Study design and participants

For this academic, multicentre, placebo-controlled, parallel-group, single-blind trial we recruited patients with autosomal dominant polycystic kidney disease referred to outpatient clinics of five hospitals in Italy (Azienda Ospedaliera Papa Giovanni XXIII, Bergamo; Università Federico II, Naples; Presidio Ospedaliero V Fazzi, Lecce; Ospedale Ca' Foncello Treviso; and IRCCS Ospedale Maggiore Policlinico Mangiagalli e Regina Elena, Milan). Adult (>18 years) men and women, with a clinical and ultrasonographic diagnosis of autosomal dominant polycystic kidney disease according to Ravine criteria,[11] and estimated glomerular filtration rate (GFR) of 40 mL/min per 1·73 m² or higher as calculated by the Modification of Diet in Renal Disease study four variables equation, were eligible. We excluded patients with confounding factors that could affect renal function loss independent of kidney growth and treatment allocation—ie, diabetes mellitus; urinary protein excretion rate greater than 1 g/24 h; abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease; and urinary tract lithiasis or infection. Patients with symptomatic gallstones or biliary sludge, cancer, or major systemic disease, those who were unable to provide informed consent, and pregnant, lactating, or potentially childbearing women without adequate contraception were also excluded.

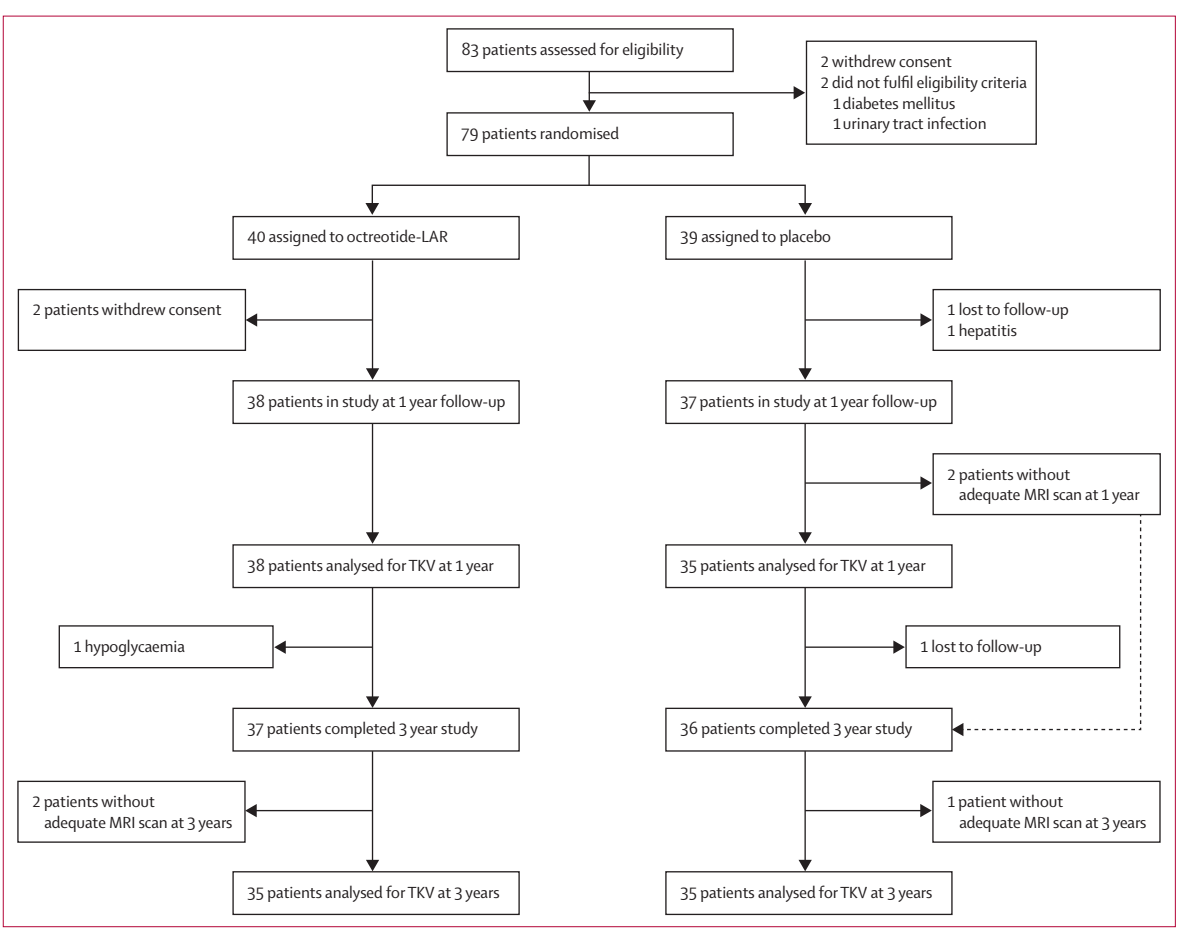

Figure 1: **Trial profile**
LAR=long-acting release. TKV=total kidney volume.

The study conformed to the principles of the Declaration of Helsinki. The institutional review board or ethics committee at each site approved the protocol; written, informed consent was obtained from all participants. The study was coordinated and monitored by the Department of Renal Medicine of the Clinical Research Centre for Rare Diseases (IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy) according to good clinical practise guidelines. Data were locally recorded in dedicated case report forms and then entered into the central database at the coordinating centre. Consolidated Statement Of Reporting Trials (CONSORT) guidelines were adhered to.[12]

For baseline assessment, participants had their blood pressure measured in the dominant arm after 5 min rest in the sitting position. The mean of the three measurements, taken 2 min apart, was recorded for statistical analyses. Blood was sampled the morning after overnight fasting for laboratory assessments, which consisted of routine haematochemistry, renal and liver function tests, and peripheral blood cell counts. 24 h urine collections were sampled for protein, albumin, sodium, creatinine, urea, glucose, phosphorus excretion, and osmolality as calculated by standard formula. Additionally, protein to creatinine ratio was assessed in spot morning urine samples. GFR was measured by iohexol plasma clearance technique,[13] and sample assays were centralised at the IRCCS—Istituto di Ricerche Farmacologiche Mario Negri. TKV, total cyst volume (TCV), and non-cyst kidney volume (NCV) were quantified by non-contrast enhanced MRI.

	Octreotide-LAR (n=40)	Placebo (n=39)
Age (years)	36 (8)	38 (8)
Men	17 (42·5%)	20 (51·3%)
Height (cm)	170·2 (9·7)	169·7 (10·3)
Weight (kg)	70·3 (16·1)	74·8 (12·4)
Blood pressure (mm Hg)		
Systolic	127·2 (14·6)	127·2 (16·3)
Diastolic	83·5 (11·4)	83·5 (12·9)
MAP	98·1 (12·0)	98·1 (13·5)
Serum creatinine (μmol/L)	91·9 (36·2)	107·8 (41·5)
GFR (mL/min per 1·73 m²)*	86·5 (24·8)	80·2 (31·0)
eGFR (mL/min per 1·73 m²)†	90·0 (37·0)	76·1 (40·9)
Urine albumin (μg/min)	54·6 (80·3)	64·8 (76·8)
Urine proteins (g/24 h)	0·18 (0·16)	0·24 (0·24)
Osmolality (mmol/kg)	408·5 (155·1)	398·8 (119·0)
Fasting serum glucose (mmol/L)	4·3 (1·2)	4·6 (1·3)
TKV (mL)	1556·9 (1035·1)	2161·2 (1274·9)
HtTKV (mL/m)	905·8 (567·5)	1266·7 (733·9)
TCV (mL)	1073·2 (846·1)	1513·9 (1010·8)

Data are mean (SD) or n (%). LAR=long-acting release. MAP=mean arterial pressure. GFR=glomerular filtration rate. eGFR=estimated GFR. TKV=total kidney volume. HtTKV=height adjusted TKV. TCV=total cyst volume. *Measured by iohexol plasma clearance. †Estimated by the four-variable equation from Modification of Diet in Renal Disease study.

Table 1: **Baseline characteristics of patients**

Randomisation and masking

After baseline assessment, central randomisation by telephone was used to allocate study participants, in a 1:1 ratio, to 3 year octreotide-LAR or placebo, according to a computer-generated randomisation list. Randomisation was done by an independent investigator (GAG) at the treatment assignment secretariat (appendix). The randomisation sequence was created using SAS (version 9.0) and was stratified by centre with random block size of four and eight. Study physicians and nurses were aware of the allocated group; participants and outcome assessors were masked to allocation.

Procedures

At randomisation and every 28 days thereafter participants allocated to active treatment received two 20 mg intramuscular injections of octreotide-LAR; participants assigned placebo received two intramuscular injections of 0·9% sodium chloride solution. All participants were given best available treatment independent of treatment allocation.

After randomisation, vital signs, physical examination, and laboratory variables were assessed every 6 months together with a liver, gallbladder biliary tract, and kidney ultrasound assessment. GFR was measured by the iohexol plasma clearance technique at 1 year, 2 year, and 3 year follow-up visits. TKV, TCV, and NCV were quantified by non-contrast enhanced MRI at 1 year and 3 year visits.

Participants were encouraged to comply with dietary recommendations as per centre clinical practice. Adjustments to existing therapy were allowed to optimise systolic/diastolic blood pressure to a target of less than 130/80 mm Hg throughout the study. Concomitant changes in blood glucose concentrations and need for antidiabetic therapy were monitored as possible indicators of worsening in insulin sensitivity and glucose metabolism related to octreotide-LAR treatment.

See Online for appendix

The non-contrast enhanced MRI acquisition protocol was in line with that of the Consortium for Radiological Imaging Studies of Polycystic Kidney Disease,[14] and was set up for a 1·5 T scanner (appendix). Coronal T1-weighted and T2-weighted series covering entire kidneys were acquired in one breath-hold, with slice thickness of 3–4 mm. All images were collected in Digital Imaging and Communications in Medicine format by the coordinating centre for subsequent analysis. Kidneys were first manually outlined on coarse (5–9 mm thick) T2 MRI by a trained operator (AC) who was masked to treatment. TKV was obtained as the volume of kidney outlines. TCV was quantified from T2 MRI by an in-house, semi-automated method. NCV was computed as the difference between TKV and TCV (appendix).

The reproducibility of TKV and TCV was assessed in a set of ten participants, referred to the Bergamo centre,

who had a repeat MRI scan 15 min after repositioning; these patients were selected on the basis of their availability to undergo repeat assessments. TKV and TCV were highly reproducible, with mean inter-acquisition difference for TKV of 23 mL (SD 74; –0·2% [4·4], concordance correlation coefficient 1) and for TCV of –40 mL (84; –0·6% [4·1], concordance correlation coefficient 0·99).

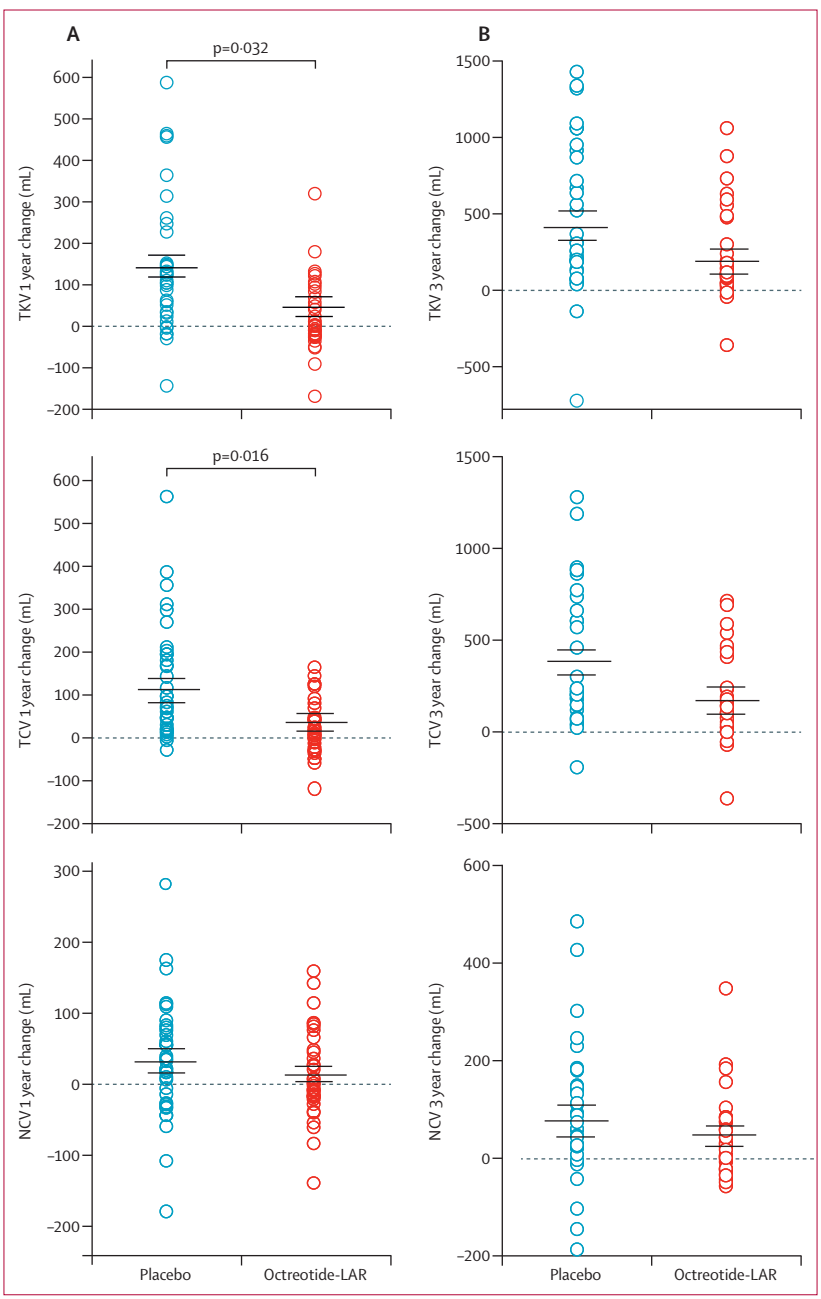

Figure 2: **Renal volume changes during placebo or octreotide-LAR treatment**
Absolute change in TKV, TCV, and NCV at 1 year (A) and at 3 years (B) of treatment compared with baseline. Circles denote individual values, long lines are mean values and short lines are SEM. p values from ANCOVA. LAR=long-acting release. TKV=total kidney volume. TCV=total cyst volume. NCV=non-cyst volume.

Statistical analysis

Sample size was estimated for the main prespecified outcome variable, absolute TKV change, assuming a two group *t* test (two-sided) of the difference between octreotide-LAR and placebo. On the basis of the pilot study,[9] a mean increase of 162 mL (SD 114) was expected in the placebo group over 3 year follow-up, and octreotide-LAR treatment was predicted to reduce such an increase by 50% (ie, from 162 mL to 81 mL). On the basis of these assumptions, a sample size of 33 evaluable participants per group (total sample size 66) would give the trial an 80% power to detect as statistically significant (α=0·05, two-tailed test) the expected difference in TKV change between the two treatment groups over 3 years. To account for 15% dropout, we planned to include 39 participants per group.

The primary endpoint was change in TKV, as measured by MRI, at 1 year and 3 year follow-up. Secondary endpoints were changes in TCV and NCV, GFR, and safety variables, including vital signs, clinical laboratory tests, and adverse events.

All statistical analyses were done by modified intention-to-treat , using SAS (version 9.1) and STATA (version 12). Changes in TKV, height-adjusted TKV (htTKV), TCV, and NCV at 1 and 3 years and all other between-group effects were assessed by ANCOVA, adjusted for baseline measurement. TKV, htTKV, TCV, and NCV slope and GFR decline were assessed with a linear regression analysis and compared with the Wilcoxon rank-sum test. A linear mixed-model was used for TKV, htTKV, TCV, NCV, and GFR repeated measures, with baseline value, study site, age, and sex as covariates. Within-group comparisons were assessed by paired *t* tests, repeated-measures ANOVA, or McNemar test. Correlations were tested with Pearson's *r* correlation coefficient. One interim efficacy comparison was done by the Data and Safety Monitoring Board 2 years after the last participant was randomised, using the group sequential O'Brien and Fleming approach as an early stopping guideline for efficacy. The potential effect of missing data was assessed with multiple imputation by chained equations (ice command in STATA 12).

Data were expressed as mean (SE), median (IQR), or number (%) unless otherwise specified. GFR was log-transformed before statistical analysis. All p values were two sided. This trial is registered with ClincalTrials.gov, number NCT00309283.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Eligible participants were enrolled in the study from April 27, 2006, to May 12, 2008. Of 83 screened participants,

	Octreotide-LAR			Placebo			p value
	Baseline (n=38)	1 year (n=38)	3 year (n=35)	Baseline (n=37)	1 year (n=37)	3 year (n=35)	
TKV							
Mean (mL)	1556·9 (167·9)	1603·1 (176·1)	1672·7 (202·0)	2161·2 (209·6)	2304·9 (224·6)	2621·0 (271·0)	..
Absolute change (mL)	..	46·2 (18·2)	220·1 (49·1)	..	143·7 (26·0)	454·3 (80·8)	0·032*; 0·25†
Annual slope (mL per year)	..	..	76·6 (16·8)	..	..	152·0 (27·4)	0·0085
HtTKV							
Mean (mL/m)	905·8 (92·1)	932·3 (96·7)	970·1 (109·2)	1266·7 (120·7)	1350·4 (128·8)	1535·2 (156·0)	..
Absolute change (mL/m)	..	26·4 (10·3)	125·5 (27·8)	..	83·6 (14·9)	264·9 (47·1)	0·030*; 0·23†
Annual slope (mL/m per year)	..	..	43·7 (9·5)	..	..	88·6 (16·0)	0·0078
TCV							
Mean (mL)	1073·2 (141·0)	1078·02 (146·9)	1136·4 (166·6)	1513·9 (168·5)	1591·4 (179·4)	1876·5 (218·5)	..
Absolute change (mL)	..	33·0 (14·7)	183·8 (41·7)	..	108·5 (18·3)	394·7 (62·9)	0·017*; 0·11†
Annual slope (mL per year)	..	..	64·4 (14·3)	..	..	133·2 (21·4)	0·0076
NCV							
Mean (mL)	546·7 (38·4)	556·7 (38·6)	571·1 (45·7)	679·8 (54·9)	713·5 (58·0)	744·5 (67·1)	..
Absolute change (mL)	..	13·4 (10·2)	45·0 (14·6)	..	35·0 (13·7)	67·1 (36·3)	0·34*; 0·71†
Annual slope (mL per year)	..	..	15·4 (4·7)	..	..	21·5 (12·4)	0·12

Data are mean (SE). Annual slopes compared by Wilcoxon rank sum test. All other comparisons performed by ANCOVA adjusting for baseline value. LAR=long-acting release. TKV=total kidney volume. HtTKV=height adjusted TKV. TCV=total cyst volume. NCV=non-cyst volume. *Octreotide-LAR versus placebo at 1 year. †Octreotide-LAR versus placebo at 3 years.

Table 2: **Kidney volume and cyst volume at baseline, and 1 year and 3 year follow-up**

two withdrew consent and two did not fulfil selection criteria (one concomitant diabetes, one urinary tract infection). 40 participants were randomly assigned to octreotide-LAR and 39 to placebo (figure 1). After randomisation, two participants in the octreotide-LAR group withdrew consent before receiving study drug, two participants in the placebo group were lost to follow-up, and one participant per group withdrew because of a serious adverse event (figure 1). Thus 73 participants (37 octreotide-LAR, 36 placebo) completed the 3 year study and were available for final analysis. However, three of 73 participants had no evaluable TKV data (two octreotide-LAR, one placebo) at 3 year follow-up because of inadequate MRI acquisition. Demography and baseline clinical and laboratory characteristics were much the same between groups, except for TKV and TCV, which were larger in the placebo group (table 1, appendix). Compliance to study drug exceeded 95% in both groups.

Over the 3 year study, TKV decreased in 15 participants in the octreotide-LAR group and increased in 20; TKV decreased in six participants in the placebo group, and increased in 29 (p=0·019). Analysis at 1 year follow-up by ANCOVA showed that absolute TKV increased significantly less (p=0·032) in the octreotide-LAR group compared with the placebo group (figure 2A, table 2). At 3 year follow-up, mean TKV increase in the octreotide-LAR group was numerically smaller than in the placebo group, but the difference in TKV growth between groups was not significant (figure 2B, table 2). Rate of TKV growth was 75·36 mL per year (95% CI 11·25–139·46) slower in the octreotide-LAR group than in the placebo group (figure 3, table 2); comparison by Wilcoxon rank-sum test showed that the difference was significant (p=0·0085). We obtained much the same results when absolute increases in TKV at 1 year and 3 year follow-up and yearly increases averaged during the study were adjusted by the participant's height (htTKV; table 2). Percentage increase in TKV was significantly smaller in the octreotide-LAR group than in the placebo group at 1 year (median 0·75% [IQR –2·16 to 6·35] *vs* 6·64% [2·90 to 11·12]; p=0·0018) and at 3 years (10·87% [5·00 to 22·78] *vs* 19·89% [12·17 to 30·44]; p=0·0416; figure 4).

At 1 year follow-up, absolute TCV increased significantly less (p=0·016) in the octreotide-LAR group compared with the placebo group (figure 2A, table 2). At 3 year follow up, mean TCV increase in the octreotide-LAR group was numerically smaller than in the placebo group, but the difference was not significant (figure 2B, table 2). Rate of TCV growth was 68·77 mL per year (95% CI 17·26–120·44) slower in the octreotide-LAR group than in the placebo group (p=0·0076; figure 3, table 2). Percentage increase in TCV was significantly smaller in the octreotide-LAR group than in the placebo group at 1 year (median 2·36% [IQR –2·17 to 6·84] *vs* 7·02% [2·29 to 11·14]; p=0·0135) but not at 3 years (15·51% [6·14 to 36·11] *vs* 24·59% [14·09 to 34·54]; p=0·153). NCV growth did not significantly differ between treatment groups either at 1 year or 3 year follow-up (table 2).

Compared with baseline, measured GFR[13] decreased by 10·8% in the octreotide-LAR group and by 9·7% in the placebo group after 1 year of treatment (table 3).

Thereafter, mean GFR values remained stable in participants in the octreotide-LAR group, whereas they progressively decreased in participants in the placebo group, up to 3 year follow-up (table 3). Percentage GFR reduction compared with baseline was numerically smaller in the octreotide-LAR group than in the placebo group from 1 year onward, but the difference was not significant (figure 5). Over the whole follow-up period, rate of GFR decline tended to be slower in the octreotide-LAR group than in the placebo group (3·85 *vs* 4·95 mL/min/1·73 m² per year), but the difference was not significant (table 3). Short-term GFR reduction at 1 year was much the same between groups (figure 5), but subsequent chronic GFR decline from year 1 to 3 was almost 50% slower in the octreotide-LAR group than in the placebo group (2·28 *vs* 4·32 mL/min/1·73 m² per year; p=0·03; figure 5).

Explorative analyses showed a correlation between 1 year GFR reduction and subsequent chronic GFR decline that was negative in the octreotide-LAR group (r=–0·487, p=0·0047, log-transformed data), and positive in the placebo group (r=0·369, p=0·053, log-transformed data; figure 6). Actual TKV and TCV values at baseline (r=0·987, p<0·0001) and their changes at 3 years versus baseline (r=0·834, p<0·0001) were significantly correlated (appendix). Both TKV (r=–0·562, p<0·0001) and TCV (r=–0·52, p<0·0001) baseline values were significantly correlated with GFR values at baseline (r=–0·25, p=0·042) and with absolute GFR changes at 3 years (r=–0·26, p=0·040), whereas no significant correlation was noted between GFR changes at 3 years and TKV (r=–0·139, p=0·273) or TCV (r=–0·167, p=0·198) values at 3 year follow-up.

At 1 year, bodyweight, diastolic and mean blood pressure, serum urea concentration, and red cell count and haemoglobin concentration were significantly lower in participants in the octreotide-LAR group than in those in the placebo group (appendix). All other haematochemical and urinary variables, including 24 h urinary output, and urea, phosphate, and sodium excretion, were much the same in the two groups (appendix). We noted no significant difference between octreotide-LAR and placebo for any measured variables at 3 year follow-up. Blood pressure lowering drugs were similarly distributed between the two treatment groups at inclusion, but were more frequently needed in the placebo group after randomisation. Other drugs were equally distributed in the two treatment groups at baseline and on subsequent follow-up (appendix).

37 (92·5%) participants in the octreotide-LAR group and 32 (82·1%) in the placebo group had at least one adverse event (p=0·163). Participants with serious adverse events

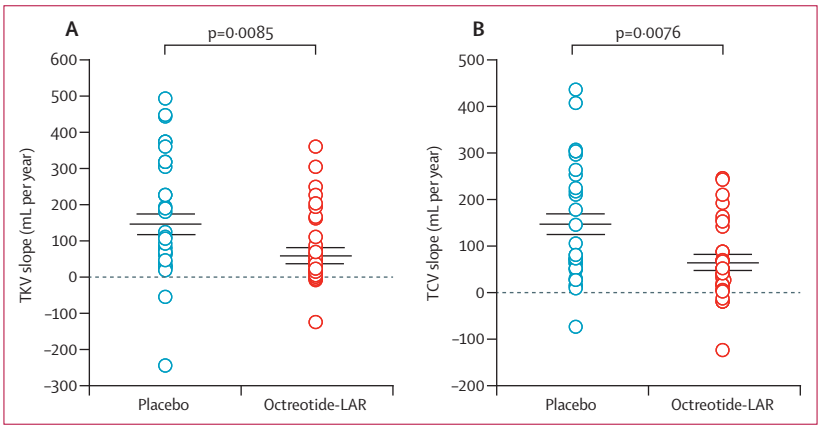

Figure 3: **Rate of renal volume growth during placebo or octreotide-LAR treatment**
Annual rate of growth in TKV (A) and TCV (B) in the two treatment groups. Circles denote individual values, long lines are mean values and short lines are SE. p values from Wilcoxon rank sum test. LAR=long-acting release. TKV=total kidney volume. TCV=total cyst volume. NCV=non-cyst volume.

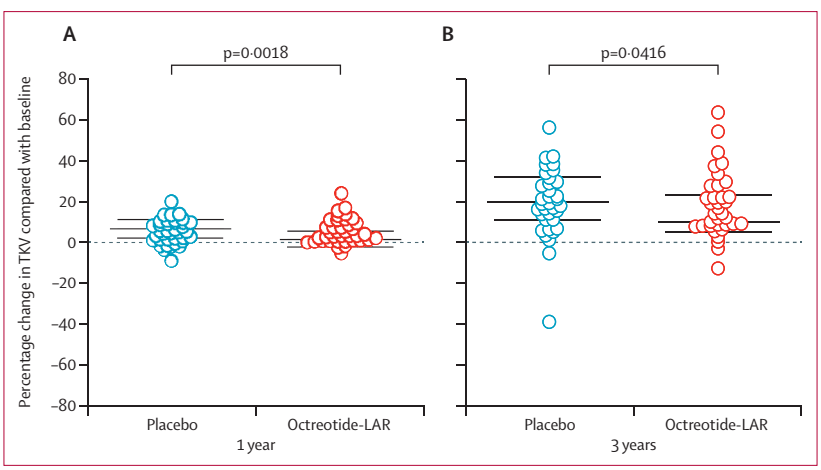

Figure 4: **Percentage change in TKV during 3 year study period**
Percentage change compared with baseline at 1 year (A) and 3 years (B) of treatment with placebo or octreotide-LAR. Circles denote individual values, long lines are median and short lines are IQR. p values from unpaired *t* test. LAR=long-acting release. TKV=total kidney volume.

	Octreotide-LAR				Placebo			
	Baseline (n=36)	1 year (n=34)	2 year (n=34)	3 year (n=36)	Baseline (n=34)	1 year (n=32)	2 year (n=33)	3 year (n=31)
Mean (mL/min per 1·73m²)	88·68 (3·93)	77·86 (4·23)	78·50 (4·82)	76·33 (4·66)	77·77 (5·30)	72·16 (5·45)	67·98 (6·28)	64·64 (6·51)
Annual slope (mL/min per 1·73m² per year)								
0–3 years	..	..	..	–3·85* (–6·20 to –1·92)	..	..	..	–4·95 (–7·49 to –1·97)
1–3 years	..	..	..	–2·28† (–5·34 to 0·43)	..	..	..	–4·32 (–7·77 to –1·19)

Data are mean (SE) or median (IQR). LAR=long-acting release. *Wilcoxon rank sum test p versus placebo=0·13. †Wilcoxon rank sum test p versus placebo=0·027.

Table 3: **Glomerular filtration rate at baseline, and 1 year, 2 year, and 3 year follow-up**

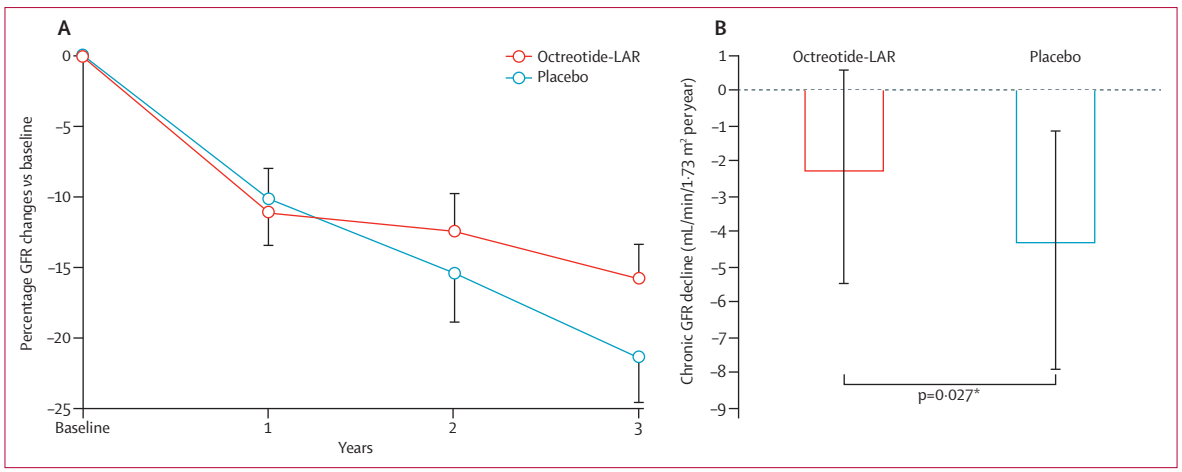

Figure 5: **Effect of placebo or Octreotide-LAR treatment on kidney function**
Percentage change in GFR, measured by iohexol plasma clearance, compared with baseline in placebo and Octreotide-LAR groups during the 3 year treatment (A). Chronic GFR decline from year 1 to year 3 after randomisation in the two treatment groups (B). Values are mean (SEM) and median (IQR). p values calculated after log-tranformation of GFR values. p values from Wilcoxon rank-sum test. GFR=glomerular filtration rate.

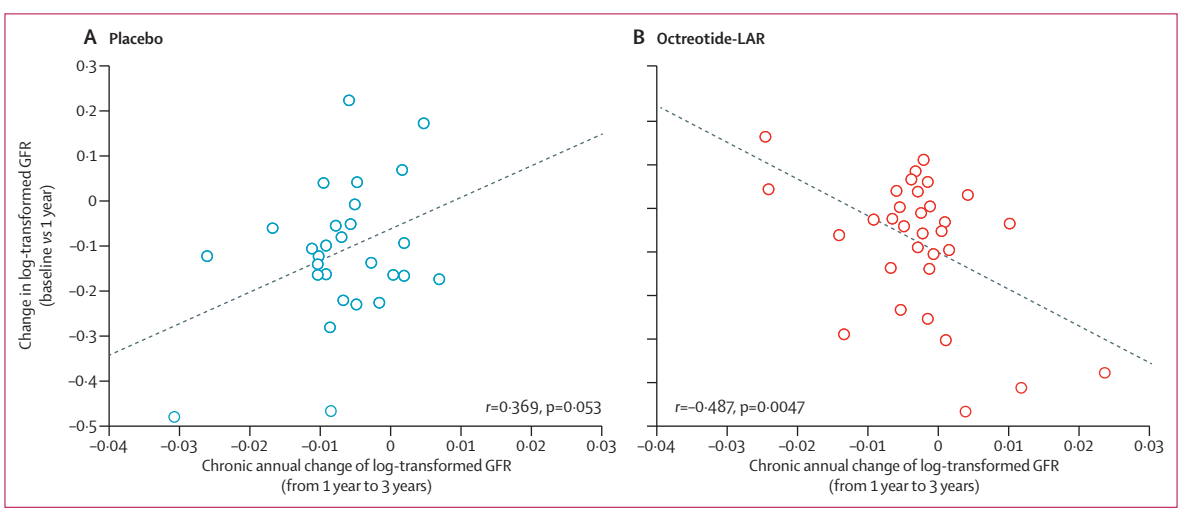

Figure 6: **Correlation between individual 1 year GFR changes and subsequent chronic GFR decline in placebo and octreotide-LAR groups**
1 year changes and subsequent GFR slopes were calculated after log-transformation of GFR values. p values from Pearson *r* correlation coefficient. GFR=glomerular filtration rate.

were similarly distributed in the two treatment groups (table 4). However, four cases of cholelithiasis or acute cholecystitis occurred in the octreotide-LAR group and were probably treatment-related (table 4). Non-serious adverse events were more frequent in the octreotide-LAR group because of an excess of events, such as asymptomatic cholelithiasis, diarrhoea, flatulence, abdominal pain, or hypoglycaemia, which seemed to be treatment-related in most cases, whereas disease-related events, such as kidney or back pain, urinary tract infections, and nephrolithiasis seemed to be more frequent in the placebo group (appendix). All gastrointestinal symptoms were transient, self-limiting, and spontaneously recovered within the first month of treatment. A uterine leiomyoma was noted in five participants in the octreotide-LAR group. Hypoglycaemic episodes were reported in two participants in the octreotide-LAR group; one patient needed treatment for this event and discontinued the study drug 6 months after randomisation because of persistent hypoglycaemia. All other participants received the full dose of octreotide-LAR throughout the study, except one participant who continued on a half dose 6 months after randomisation because of a hand tremor.

Discussion

3 year treatment with octreotide-LAR slowed kidney volume growth in adult participants with autosomal dominant polycystic kidney disease and large kidney volumes with preserved or moderately impaired renal function. The slower growth in TKV in the octreotide-LAR group was associated with slower growth in TCV, whereas changes in NCV did not differ between groups.

	Octreotide-LAR (n=40)	Placebo (n=39)
Overall	6 (15·0%)	7 (18·0%)
Sepsis	1 (2·5%)	2 (5·1%)
Cholelithiasis	2 (5·0%)	0
Acute cholecystitis	2 (5·0%)	0
Gastroenteritis	0	1 (2·6%)
Hepatitis C	0	1 (2·6%)
Haemorrhagic hepatic cyst	1 (2·5%)	0
Nephrolithiasis	0	1 (2·6%)
Renal cyst haemorrhage	1 (2·5%)	1 (2·6%)
Urinary tract infection	2 (5·0%)	1 (2·6%)
Intracranial aneurysm	1 (2·5%)	0
Hypertensive crisis	0	1 (2·6%)
Acute worsening of chronic renal dysfunction	0	1 (2·6%)
Spinal column injury	0	1 (2·6%)

Data are n (%). Excludes one foot fracture and one pregnancy in the octreotide-LAR group. LAR=long-acting release.

Table 4: **Patients with at least one serious adverse event**

TKV and TCV at baseline and their changes at follow-up were significantly correlated. GFR decreased in the two treatment groups during the first year of follow-up. Thereafter, however, it stabilised in the octreotide-LAR group, whereas it progressively declined in the placebo group; the difference in rate of renal function loss was significantly different between groups. Notably, in the octreotide-LAR group, initial short-term GFR reduction was inversely correlated with subsequent GFR decline, thus participants with the largest initial reductions seemed to be those who were more effectively protected from progressive renal function loss in the long-term. Treatment was safe and well tolerated in all participants.

Consistent with previous findings in patients with autosomal dominant polycystic kidney disease receiving long-term treatment with the V_2 receptor antagonist tolvaptan,[15] the protective effect of octreotide-LAR against TKV growth was larger in the first year of treatment than at subsequent follow-up. The explanation for biphasic changes in kidney volumes might be dual: first, on prolonged exposure to octreotide-LAR, somatostatin receptors might progressively down-regulate or desensitise, probably via endocytosis of the receptor-ligand complex,[16] which might translate into reduced treatment-effect in the long-term; second, fluid secretion into cysts might acutely decrease shortly after initiation of octreotide-LAR treatment, and then stabilise by subsequent follow-up, which might result in an acute initial cyst shrinkage followed by slower cyst volume reduction with long-term treatment. This hypothesis is supported by evidence that in patients with autosomal dominant polycystic kidney disease, a 3–4% reduction in TKV was noted within 1–3 weeks of treatment with tolvaptan,[17] a drug shown to share with somatostatin a similar inhibitory effect on cyst-cell fluid secretion in vitro.[18] Independent of different possible mechanisms mediating treatment effect over time, the finding that the rate of TKV growth averaged throughout the study was about 50% slower in the octreotide-LAR group than in the placebo group provides convincing evidence of a sustained benefit of long-term somatostatin treatment.

The volume of tubular cysts accounts for a large part of the total volume of polycystic kidneys. Thus, any change in TKV over time is largely explained by concomitant changes in cyst volumes. By using an innovative and reproducible processing of MRI for estimation of TCV, we have shown that the protective effect of octreotide-LAR treatment against TKV growth was paralleled by a concomitant and equivalent protective effect against the growth of TCV compared with placebo. Octreotide-LAR treatment might slow cyst growth by inhibiting both fluid secretory and proliferative properties of cyst epithelial cells through SSTR-mediated inhibition of cAMP production in distal nephrons and collecting ducts.[6,19]

We used a gold-standard technique for serial GFR measurements[13] and showed that slower kidney and cyst volume growth during octreotide-LAR treatment was associated with slower renal function loss over time. The finding that, after an initial reduction, GFR almost stabilised up to study end, allows us to predict[20] that in the long-term, octreotide-LAR will slow the progressive renal function loss that can eventually result in end-stage renal disease and need for renal replacement therapy. Octreotide is known to acutely decrease GFR in healthy individuals,[21] and in patients with type 1 diabetes[22] or liver cirrhosis[23] by hemodynamic mechanisms that are probably mediated by inhibited growth hormone secretion and action.[24] Thus, in patients with autosomal dominant polycystic kidney disease this effect might contribute to blunt the compensatory hyperfiltration of glomeruli surviving the disruptive effects of uncontrolled cyst growth.[25] This finding might have clinical implications since long-term glomerular hyperfiltration can cause premature glomerular obsolescence with worsening proteinuria, declining filtration power, and eventually glomerulosclerosis,[26,27] events that almost invariably accompany the course of autosomal dominant polycystic kidney disease, in particular in the most advanced stages characterised by accelerated loss of renal function.[1] Thus, octreotide-LAR treatment might be renoprotective in patients with this disorder, not only by preventing cyst growth but also by inhibiting the maladaptive events sustained by, and contributing to, progressive nephron loss.

Reductions in blood pressure and bodyweight noted in the octreotide-LAR group compared with placebo are probably indicative of slower renal function loss and growth-hormone and cortisol-inhibited production and activity that translated into less water and salt retention in patients on active treatment.[24] Concomitant reductions in haematocrit and haemoglobin concentration might

result from impaired erythropoiesis secondary to growth hormone inhibition.[27]

Notably, all study participants were given best available treatment independent of treatment allocation and the study findings could not be explained by more intensified antihypertensive therapy, dietary protein and salt restriction, or more liberal water intake in the octreotide-LAR group, since the use of blood-pressure lowering drugs was more common in the placebo group and 24 h urinary output, and urea, phosphate, and sodium excretion were much the same between groups throughout the study. Data did not seem to be confounded by a treatment-centre effect (data not shown).

Consistent with previous reports, biliary tract disease seemed to be the most clinically relevant complication related to treatment.[28] However, it was asymptomatic in most cases and never needed treatment withdrawal. Diarrhoea, which was recorded in 14 participants in the octreotide-LAR group and in four in the placebo group, was non-serious and spontaneously recovered in all patients within the first month of treatment. Uterine leyomiomas was unexpectedly recorded in five women in the octreotide-LAR group and was probably a casual finding, since leyomioma has never been reported as a possible treatment-related effect, and somatostatin is among pharmacological treatments used for this disorder.[29] Self-limiting hypoglycaemic episodes were noted in two participants in the octreotide-LAR group, which in one patient needed treatment discontinuation. This was an unexpected finding since this side-effect was not previously noted with octreotide-LAR, furthermore, this treatment has been occasionally reported to increase blood glucose or HbA_{1C} concentrations. We did not identify these events in our participants.

Together, our safety findings suggest that octreotide-LAR was safe and well tolerated in all participants. This finding contrasts other drugs so far tested in autosomal dominant polycystic kidney disease—such as tolvaptan, which had serious side-effects, including irreversible and potentially fatal liver toxicity, and the MTOR inhibitors sirolimus and everolimus—which have been abandoned for treatment of this disorder.[29] Thus, because of their very good risk–benefit profile, even in life-long therapy,[10] somatostatin analogues are so far the only viable option for long-term treatment of this disorder.

Major limitations of this study were small sample size and short follow-up, which were both dictated by fund and drug restrictions typical of independent trials. We did not assess participant quality of life. Only white patients were included, thus whether data can be generalised to other ethnic groups is unknown. Adjustments for baseline TKV and TCV by ANCOVA and comparisons between their percentage changes versus baseline confirmed that differences between treatment groups were significant independent of differences in baseline volumes. Parametric, multiple imputations by chained equations confirmed that study findings were robust to missing data. This independent trial is rare in a scenario dominated by company-sponsored trials which, because of the large statistical power achieved by inclusion of hundreds or even thousands of patients, detected as statistically significant effects of treatment that are, at best, clinically uncertain, particularly when assessed alongside treatment-related side-effects.[15,29,31–33] Our use of gold standard procedures, including centralised MRI processing, allowed us to show a clinically relevant 50% reduction in kidney growth despite the small sample size, a finding that was in line with the hypothesised treatment effect at the time of sample size estimation. Involvement of academic reference centres was an additional guarantee that treatment effect was achieved in addition to results of best available therapy.

As far as we are aware, this is the first randomised clinical trial of a somatostatin analogue assessing the long-term treatment effect on kidney growth as the primary endpoint; by contrast other studies primarily focused on livers with polycystic disease from different causes and assessed the effect on kidney volumes with secondary, post-hoc analyses in small subgroups of participants with renal cysts followed up for only 6 months to 1 year (panel).[34–36]

The direct measurement of GFR by the iohexol plasma clearance technique[13] allowed us to detect a clinically relevant treatment effect on GFR decline. Conceivably, with longer follow-up the measured effect on GFR slope would have translated into a protective effect against progression to terminal kidney failure.[20] Compared with

***Panel*: Research in context**

Systematic review

We searched Medline and PubMed for articles published in any language between July 1, 2005, when our feasibility pilot study was reported,[9] and Jan 31, 2013, with the keywords "somatostatin", "somatostatin analogue", "long-acting somatostatin", "octreotide" or "lanreotide" and "polycystic kidney disease", "polycystic liver disease", "PKD" or "ADPKD" and "randomised", "treatment", or "trial". Excluding our pilot study,[9] three reported randomised, double-blind, placebo-controlled clinical trials assessed the effect of a somatostatin analogue on change in total liver volume as the primary endpoint with a short treatment period.[34–36] We identified no systematic reviews or meta-analyses.

Interpretation

As far as we are aware, this study is the first to assess the long-term (3 years) effect of a long-acting somatostatin analogue treatment in a multicentre randomised, single-blind, placebo-controlled, parallel-group trial, with change in total kidney volume (TKV) as the primary outcome. It also provides new information about the effect of a somatostatin analogue on total renal cyst growth. The results show that 3 year octreotide-LAR therapy compared with placebo slowed the increase in TKV by blunting the growth of cyst volume in participants with autosomal dominant polycystic kidney disease and stabilised renal function, with a safety profile that was good compared with that of other drugs tested in this context. There are presently no proven treatments for this disorder and an effective disease modifying therapy such as octreotide-LAR could have important implications for these patients in providing a novel, safe, and favourable preventive approach to disease progression.

previous ADPKD trials that used unreliable GFR estimates,[37] this was another strength of our study. The association that we identified between larger short-term GFR reduction and slower long-term GFR decline with octreotide-LAR treatment provided novel insights into the mechanisms—ie, amelioration of glomerular hyperfiltration[24]—possibly underlying the long-term renoprotective effect of somatostatin in this context and might help to adequately design and power future trials with long-term GFR decline as the primary outcome.

Octreotide-LAR should be tested in larger trials adequately powered to detect its protective effect against progression to end-stage kidney disease with consequent improvement in patients' quality of life.

Contributors

GR, PR, NP, and AR had the original idea and wrote the study protocol; NP, AP, BV, PM, RC, ADP, EB, MD, and SP identified, treated, and monitored study participants and contributed to data recording; PB, MI, MM, and LC did all MRI acquisition; LA, AC, and AR designed the MRI acquisition protocol, monitored MRI quality, and set up and did central image processing and renal volume quantification; FG and FC did centralised assays of, and contributed to, data recording of plasma clearance of iohexol as measurement of glomerular filtration rate; NP, AC, PR, and GR contributed to data analyses and interpretation and wrote the first draft and final version of the report; AP did the statistical analyses; and NR monitored the study. All authors had direct access to original data, critically revised the draft, and approved the final report.

Conflicts of interest

We declare that we have no conflicts of interest.

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