Effects of Octreotide–Long-Acting Release Added-on Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease: Pilot, Randomized, Placebo-Controlled, Cross-Over Trial

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Abstract

Background Tolvaptan and octreotide–long-acting release (LAR) have renoprotective effects in autosomal dominant polycystic kidney disease (ADPKD) that are partially mediated by amelioration of compensatory glomerular hyperfiltration. We compared the effects of tolvaptan and octreotide-LAR combination therapy versus those of tolvaptan monotherapy in patients with ADPKD.

Methods This pilot, randomized, placebo-controlled, cross-over trial primarily compared the effects of 1- and 4-week treatments with octreotide-LAR (two 20-mg i.m. injections) or placebo (two i.m. 0.9% saline solution injections) added-on tolvaptan (up to 90 and 30 mg/d) on GFR (iohexol plasma clearance) in 19 consenting patients with ADPKD referred to a clinical research center in Italy. Analyses were intention-to-treat. The local ethical committee approved the study.

Results At 4 weeks, GFR significantly decreased by a median (interquartile range) of 3 (−1 to 5) ml/min per 1.73 m^2 with tolvaptan and placebo ($P=0.01$) and by 7 (3–14) ml/min per 1.73 m^2 with tolvaptan and octreotide-LAR ($P=0.03$). GFR changes during the two treatment periods differed by 2 (−5 to 14) ml/min per 1.73 m^2 ($P=0.28$). At 1 week, GFR significantly decreased by 3 (0–7) ml/min per 1.73 m^2 with tolvaptan and placebo ($P=0.006$) and by 10 (−6 to 16) ml/min per 1.73 m^2 with tolvaptan and octreotide-LAR add-on therapy ($P<0.001$). GFR changes during the two treatment periods significantly differed by 3 (0–12) ml/min per 1.73 m^2 ($P=0.012$). Total kidney volume nonsignificantly changed by 4 (−48 to 23) ml with tolvaptan and placebo ($P=0.74$), whereas it decreased significantly by 41 (25–77) ml with tolvaptan and octreotide-LAR ($P=0.001$). Changes during the two treatment periods differed by 36 (0–65) ml ($P=0.01$). Octreotide-LAR also attenuated ($P=0.02$) the aquaretic effect of tolvaptan. Treatments were well tolerated.

Conclusions In patients with ADPKD, octreotide-LAR added-on tolvaptan reduced GFR more effectively than octreotide-LAR and placebo. Octreotide-LAR also reduced total and cystic kidney volumes and attenuated the acquaretic effect of tolvaptan.

Clinical Trial registry name and registration number: Tolvaptan-Octreotide LAR Combination in ADPKD (TOOL), NCT03541447.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a leading cause of kidney failure worldwide. Elevated levels of 3′, 5′-cyclic adenosine monophosphate (cAMP) play a central role in the pathogenesis and progression of the disease.[1–3] Vasopressin antagonists and somatostatin analogs, which indirectly reduce adenyl cyclase 6 activity, markedly reduce kidney tubular cell proliferation and cyst growth in experimental models of ADPKD, an effect that is associated with reduction in kidney cAMP levels with both medications.[1,4] In combination, the two treatments show a clear additive effect and may significantly reduce kidney cystic and fibrotic volume and cAMP levels to wild-type levels.[5]

The vasopressin antagonist tolvaptan and the somatostatin analog octreotide–long-acting release (LAR) effectively slow total kidney volume (TKV) and cystic kidney volume growth and GFR decline in patients with ADPKD.[6,7] Moreover, with both medications changes in TKV, cystic kidney volume and GFR show a biphasic trend, with a larger acute (and reversible) reduction that can be observed within

weeks or months[8–10] followed by a chronic effect that progressively manifests over years of follow-up,[6,7] even in patients with stage 4 CKD.[11] The effect on TKV and cystic kidney volume is larger during initial treatment possibly because fluid secretion into cysts acutely decreases shortly after the initiation of treatment[8–10] and then it stabilizes on subsequent follow-up. This might lead to an acute initial cyst shrinkage followed by a slower cyst volume reduction upon chronic treatment exposure that would be predominantly mediated by inhibited tubular cell proliferation. The effect on GFR is also biphasic with an initial reduction that appears to be mediated by amelioration of compensatory hyperfiltration[7–10] of glomeruli surviving cyst-induced structural damage[12] followed by a slower decline long term that is most likely mediated by inhibited kidney cyst growth which, combined with amelioration of glomerular hyperfiltration, contributes to protect the kidney from progressive healthy parenchyma disruption. Conceivably, these hemodynamic effects are not shared by other somatostatin analogs such as lanreotide[13] that showed no renoprotective effects in ADPKD patients with stage 3 CKD.[14] Data on tolvaptan show that short-term GFR reduction is a hemodynamic phenomenon that is largely sustained by a concomitant reduction in renal plasma flow.[9]

On the basis of experimental data,[5] it is conceivable that tolvaptan and octreotide-LAR should also have an additive effect in human disease. Thus, initial GFR, TKV, and cystic kidney volume reduction should be larger with tolvaptan and octreotide-LAR combination therapy than with tolvaptan or octreotide-LAR monotherapy. To address this working hypothesis, we conducted a pilot trial to compare the short-term effects of tolvaptan and octreotide combination therapy with those of tolvaptan combined to placebo on directly measured GFR,[15] TKV, cystic kidney volume, and kidney functional parameters as assessed by magnetic resonance imaging in a homogeneous cohort of patients with ADPKD.

Methods

TOOL was "A Pilot, Phase II Study with a Prospective, Randomized, Cross-Over, Placebo-Controlled, Double-Blind Design to Assess the Short-Term Effects of Tolvaptan plus Placebo vs Tolvaptan plus Octreotide-LAR Combination Therapy in ADPKD Patients with Normal Kidney Function or Hyperfiltration" (Supplemental Figure 1). The study was registered at ClinicalTrials.gov NCT03541447 and at EudraCT n. 2017.004701-40 and was approved by the Ethical Committee of the Azienda Socio-Sanitaria Territoriale (ASST) Papa Giovanni XXIII. All participants provided written informed consent to study participation.

Potentially eligible patients were identified from the database of the ADPKD Outpatient Clinics of the Unit of Nephrology of the ASST and were referred to the Clinical Research Center for Rare Diseases Aldo e Cele Daccò of the Istituto di Ricerche Farmacologiche Mario Negri IRCCS in Ranica (Italy). Female and male patients with clinical and ultrasonographic diagnosis of ADPKD, serum creatinine $\leq$1.0 and $\leq$1.2 mg/dl, respectively, changes in serum creatinine $<$30% over the past year, and no evidence of other kidney or systemic diseases entered a 2-week screening phase. Remaining inclusion criteria and all exclusion criteria are detailed in the Supplemental Material.

After screening evaluation, any concomitant treatment with drugs that may affect glomerular hemodynamics was stopped. Patients with creatinine clearance persistently $\geq$80 ml/min per 1.73 m^2 2-week apart, no evidence of urinary and/or biliary tract infection or obstruction, or hemorrhagic or infected cysts had a direct GFR measurement (pre run-in) with the iohexol plasma clearance technique[15] and entered a 4-week run-in period. No systematic change in concomitant medications or diet was introduced during the run-in period and thereafter.

At completion of the run-in period, patients had a second GFR measurement (baseline) along with the evaluation of all tests listed in Table 1. An electrocardiogram at rest was recorded.

The day after, TKV, cystic kidney volume, renal blood flow, renal plasma flow, and other kidney functional parameters were directly measured by magnetic resonance imaging (see Supplemental Material) or calculated by standard formulas.

All patients received a first 4-week treatment period with tolvaptan. Tolvaptan was started at the dose of 45 mg in the morning and 15 mg in the afternoon. Then, morning and afternoon doses were up-titrated every 2 days to 60 and 30 mg and then to 90 and 30 mg, respectively, according to tolerability. By completion of this 4-week titration period, participants were randomly allocated using a 1:1 randomization ratio to 4-week treatment periods with tolvaptan. During these two treatment periods, tolvaptan was administered at the maintenance dose achieved at the end of the titration period. According to the randomization plan, at the start of one of the two treatment periods, tolvaptan was combined with two 20-mg i.m. injections of octreotide-LAR, whereas at the start of the other treatment period, tolvaptan was combined with two i.m. injections of 0.9% NaCl solution (placebo for octreotide-LAR). Routine baseline parameters and the GFR were measured at treatment day 7 ($\pm$1). Then, baseline parameters were re-evaluated at the end of the 4-week treatment period, and each patient entered a 4-week washout period. At the end of the 4-week washout period, the baseline evaluations were repeated, and each patient crossed-over to the other treatment arm (Supplemental Figure 1) for the second 4-week treatment period with tolvaptan (again, at the same maintenance dose achieved during the run-in). Routine baseline parameters and the GFR were measured at treatment day 7 ($\pm$1). Then baseline parameters were re-evaluated at the end of the second 4-week treatment period, and each patient entered a final, 4-week recovery period. At the end of this period, baseline evaluations were reassessed (final visit).

To assess treatment effect on patient quality of life, the Physical Component Summary Score and Mental Component Summary Score were evaluated at the start and end of each treatment period.

The study primarily aimed to evaluate the effect of 1- and 4-week tolvaptan and octreotide-LAR combination therapy as compared with tolvaptan and placebo combination therapy on measured GFR.[15] Secondly, the study evaluated treatment effects on TKV, cystic kidney volume, renal plasma flow, and other exploratory kidney functional and systemic parameters.

The primary and secondary efficacy variables of this cross-over study were analyzed by paired t test (or Wilcoxon signed-rank test, in case of departure from

Table 1. Baseline characteristics

Characteristic	Overall, $n = 19$	Octreotide LAR-Placebo, $n = 9$	Placebo-Octreotide LAR, $n = 10$
Demographics			
Age (yr)	41±12	44±12	38±12
Male sex, *n* (%)	10 (53)	4 (44)	6 (60)
European, *n* (%)	18 (95)	9 (100)	9 (90)
Current smokers, *n* (%)	8 (42)	4 (44)	4 (40)
Never smoked, *n* (%)	7 (37)	3 (33)	3 (30)
Former smokers, *n* (%)	4 (21)	1 (11)	3 (30)
Clinical parameters			
Diabetes, *n* (%)	7 (37)	3 (33)	4 (40)
Body mass index (kg/m^2)	24.2±3.6	24.6±4.5	23.8±2.8
Systolic BP (mm Hg)	128±8	129±8	126±9
Diastolic BP (mm Hg)	82±7	85±4	79±7
Mean BP (mm Hg)	97±6	100±5	94±6
Heart rate (bpm)	67±11	67±12	68±10
Mayo class, *n* (%)			
1A	2 (11)	0 (0)	2 (20)
1B	4 (21)	2 (22)	2 (20)
1C	5 (26)	2 (22)	3 (30)
1D	7 (37)	5 (56)	2 (20)
1E	1 (5)	0 (0)	1 (10)
Hematochemistry			
Phosphate (mg/dl)	3.2±0.4	3.3±0.3	3.2±0.4
Calcium (mg/dl)	9.0±0.2	8.9±0.2	9.0±0.2
Sodium (mEq/dl)	139±2	139±2	139±1
Potassium (mEq/dl)	3.8±0.3	3.8±0.3	3.8±0.2
Glucose (mg/dl)	88±7	92±7	85±5
Protein (g/dl)	6.6±0.4	6.4±0.4	6.7±0.3
Total cholesterol (mg/dl)	176±33	176±35	176±33
LDL (mg/dl)	113±30	112±31	115±30
HDL (mg/dl)	50±13	52±13	48±13
Triglycerides (mg/dl)	80±41	61±19	98±48
Albumin (g/dl)	3.8±0.2	3.8±0.2	3.9±0.2
Hemoglobin (g/dl)	12.7±1.4	12.7±1.3	12.7±1.5
Urine parameters			
Urinary output (ml/24 h)	1946 [1621–2608]	1733 [1360–2301]	2081 [1816–2608]
Free-water fractional clearance	−0.25±0.61	−0.28±0.46	−0.23±0.74
Protein (g/24 h)	0.10 [0.06–0.13]	0.10 [0.07–0.12]	0.08 [0.06–0.13]
Albumin (μg/min)	14 [6–24]	17 [7–23]	12 [6–34]
Sodium (mEq/24 h)	149±57	136±52	160±62
Potassium (mEq/24 h)	62±21	61±23	63±20
Urea (g/24 h)	25±8	25±9	26±7
Creatinine (mg/24 h)	1540±423	1577±445	1507±424
Kidney function parameters			
Creatinine (mg/dl)	0.9±0.1	0.9±0.2	0.8±0.1
Urea (mg/dl)	38±12	40±9	37±14
GFR (ml/min per 1.73 m^2)	85±13	83±15	86±13
CKD-EPI (ml/min per 1.73 m^2)	99±17	89±15	108±14
Creatinine clearance (ml/min)	123±25	121±26	126±26
RBF (ml/min per 1.73 m^2)	707±211	665±170	741±242
RPF (ml/min per 1.73 m^2)	431±110	410±90	447±125
RVR (dyn×s/cm^5)	11,675 [9967–14,621]	12,881 [10,959–14,105]	10,856 [7712–14,621]
FF (n/mo)	21.0±5.9	20.9±3.3	21.0±7.5
Albumin fractional clearance×10^{-5}	0.46 [0.28–0.78]	0.64 [0.38–0.78]	0.43 [0.24–0.52]
Kidney morphological parameters			
TKV (ml)	1142 [850–1859]	1648 [1086–1858]	996 [694–1483]
CKV (ml)	738 [407–1413]	1190 [636–1413]	560 [347–831]

All randomized patients considered as a whole (overall) and according to the randomization to the two sequences of treatment with octreotide-LAR followed by placebo or with placebo followed by octreotide-LAR, both on top of tolvaptan. LAR, long-acting release; bpm, beats per minute; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; RBF, renal blood flow; RPF, renal plasma flow; RVR, renal vascular resistance; FF, filtration fraction; TKV, total kidney volume; CKV, cystic kidney volume.

normality assumptions) and, in a multivariable, exploratory approach, by using a linear mixed model for repeated measures (PROC MIXED, SAS version 9.2; SAS Institute Inc., Cary, NC), with sequence, period, and treatment as fixed effects and participant as random effect. A nonsignificant ($P>0.05$) effect of the treatment*sequence interaction was cautiously interpreted as indicating absence of carry-over effects. Between-group comparisons arising from subgroup, exploratory analyses were made by analysis of covariance, adjusted for baseline measurement. All the analyses for the primary and secondary continuous variables were by modified intention-to-treat principle in all

Table 2. Clinical, laboratory, and instrumental parameters before and after the 1-month treatment period with tolvaptan and octreotide–long-acting release and before and after the 1-month treatment period with tolvaptan and placebo

Parameters	Tolvaptan and Octreotide–Long-Acting Release		Tolvaptan and Placebo		Between Treatments *P* Value
	Pre	Post	Pre	Post	
Primary and coprimary parameters					
1-month GFR (ml/min per 1.73 m^2)	85±15	78±12	83±13	79±14	0.54
1-week GFR (ml/min per 1.73 m^2)	85±15	75±11	83±13	78±13	0.07
Secondary parameters					
TKV (ml)	1295±623	1185±519	1318±623	1313±625	0.04
CKV (ml)	836±505	777±452	889±557	883±545	0.14
Other exploratory parameters					
Clinical parameters					
Systolic (mm Hg)	126±9	125±9	127±9	125±7	0.70
Diastolic (mm Hg)	801±7	81±5	80±6	81±5	0.95
Mean (mm Hg)	96±7	96±6	96±5	96±5	0.88
Heart rate (bpm)	68±10	61±8	65±11	66±9	0.02
BMI (kg/m^2)	24.0±3.7	24.0±3.9	24.2±3.8	23.9±3.9	0.90
Quality of life					
SF-36 PCS	53.1±3.7	52.0±5.2	52.6±4.5	52.1±4.7	0.97
SF-36 MCS	51.6±4.1	48.0±7.6	51.2±4.5	49.5±9.4	0.71
Hematochemistry					
Calcium (mg/dl)	9.0±0.2	9.1±0.3	9.0±0.2	9.1±0.3	0.95
Sodium (mEq/dl)	139±1	139±2	138±2	140±2	0.22
Phosphate (mg/dl)	3.2±0.4	3.4±0.5	3.1±0.4	3.3±0.5	0.26
Potassium (mEq/dl)	3.9±0.3	3.9±0.3	3.9±0.2	3.8±0.3	0.08
Glucose (mg/dl)	90±6	99±8	92±11	89±7	<0.001
Serum albumin (g/dl)	3.8±0.2	3.9±0.2	3.8±0.2	3.8±0.3	0.21
Serum proteins (g/dl)	6.6±0.4	6.7±0.4	6.6±0.3	6.6±0.3	0.32
Total cholesterol (mg/dl)	177±32	183±25	177±31	179±22	0.64
HDL (mg/dl)	50±13	50±12	48±14	48±13	0.47
LDL (mg/dl)	116±31	124±25	115±27	119±25	0.32
Urinary parameters					
Urinary output (ml/24 h)	1994 [1360–2785]	6952 [5219–8140]	1946 [1752–2221]	7670 [5468–9134]	0.05
Free-water fractional clearance	−0.14±0.78	1.78±2.36	−0.28±0.71	3.19±1.50	0.01
Sodium (mEq/24 h)	151±69	137±689	146±61	133±52	0.58
Creatinine (mg/24 h)	1526±436	1453±413	1524±455	1509±467	0.63
Potassium (mEq/24 h)	62±21	63±20	611±16	64±19	0.78
Urea (g/24 h)	25±10	234±7	26±8	24±8	0.83
Albumin (μg/min)	23±20	14±9	26±30	22±20	0.03
Proteins (g/24 h)	0.10±0.05	0.14±0.04	0.11±0.07	0.16±0.04	0.01
Kidney function parameters					
Serum creatinine (mg/dl)	0.86±0.15	0.99±0.20	0.86±0.14	0.97±0.15	0.17
Blood urea (mg/dl)	38±10	34±8	39±12	29±11	0.02
CKD-EPI (ml/min per 1.73 m^2)	98±18	86±20	99±17	88±18	0.53
Creatinine clearance (ml/min)	123±30	102±21	122±27	108±27	0.34
Albumin fractional clearance$\times 10^{-5}$	0.68±0.67	0.46±0.36	0.72±0.91	0.73±0.81	0.06
RBF (ml/min per 1.73 m^2)	753±232	703±181	690±202	753±211	0.58
RPF (ml/min per 1.73 m^2)	470±123	432±98	419±102	456±115	0.64
RVR (dyn×s/cm^5)	10,816±2969	11,704±2866	12,278±4253	11,109±3694	0.94
FF (n/mo)	19.3±3.7	18.2±2.8	20.7±5.5	18.1±5.3	0.71

All data expressed as mean±SD or as median [interquartile range]. Conversion factors for units: calcium in mg/dl to mmol/L, ×0.2495; phosphate in mg/dl to mmol/L, cholesterol (total, HDL, and LDL) in mg/dl to mmol/L, ×0.02586; triglycerides in mg/dl to mmol/L, ×0.01129. LAR, long-acting release; TKV, total kidney volume; CKV, cystic kidney volume; bpm, beats per minute; BMI, body mass index; SF-36, the Short Form-36; PCS, Physical Component Summary score; MCS, Mental Component Summary score; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; RBF, renal blood flow; RPF, renal plasma flow; RVR, renal vascular resistance; FF, filtration fraction.

participants who had at least one measurement after randomization, without imputation of missing data. Efficacy results were expressed as mean±SD or median (interquartile range) or number (percent). We used SAS version 9.4 and Stata version 15 for all the analyses. All *P* values were two-sided.

At the end of the 4-week treatment period, GFR was predicted, conservatively, to decrease by 3.5% (from 110.0 to 106.2 ml/min per 1.73 m^2) with tolvaptan and placebo and by 7% (from 110.0 to 102.3 ml/min per 1.73 m^2) with combination therapy as compared with pretreatment values (within-group SD=15 ml/min per 1.73 m^2, α=0.05, two-sided test, paired *t* test). With the above assumptions, a sample size for the main, randomized cross-over trial would require 161 participants. Considering the pilot nature of the study, we estimated that a pilot trial should have at least 9%

of the sample size of the main planned trial, using an 80% one-sided confidence.[16] Thus, 15 patients—each one exposed to both treatment periods in a random order—had to be available for final analyses. To account, conservatively, for a 20% dropout rate, 20 patients had to be included to have at least 15 patients available for final analyses of the primary outcome variable.

Results

Overall, 75 potentially eligible patients were identified and referred to the Clinical Research Center: 34 signed the written informed consent to study participation. Eleven patients interrupted previous therapy (if any) with renin-angiotensin-system inhibitors. Then, 22 eligible patients entered the run-in phase between January 22, 2019, and July 2, 2021 (Supplemental Figure 2), and 20 were finally randomized: ten to each treatment sequence. One patient never assumed any of the study drugs. Thus, 19 patients entered the two treatment sequences (Supplemental Figure 2). Their baseline characteristics (Table 1), and the distribution of concomitant medications (Supplemental Table 1), in the two treatment sequences were similar.

All parameters considered at different time points are shown in Table 2. Changes in main kidney functional and structural parameters and in systemic hemodynamic parameters are shown in Figures 1–4 and reported in detail in the Supplemental Material.

Primary and Coprimary Comparisons

Primary

The GFR was stable (Δ GFR: 0 [−5 to 4] ml/min per 1.73 m^2) during the 1-month run-in period (Figure 1A), whereas it significantly decreased by 3 (−1 to 5) ml/min per 1.73 m^2 during the 1-month tolvaptan and placebo treatment period ($P=0.01$) and by 7 (3–14) ml/min per 1.73 m^2 during the 1-month dual treatment period ($P=0.03$). GFR changes during the two treatment periods differed by 2 (−5 to 14) ml/min per 1.73 m^2. The difference, however, was not significant ($P=0.28$).

Coprimary

During the first week treatment period, the GFR significantly decreased by 3 (0–7) ml/min per 1.73 m^2 with tolvaptan and placebo therapy ($P=0.006$) and by 10 (−6 to 16) ml/min per 1.73 m^2 with dual therapy ($P<0.001$). Both changes significantly differed from the GFR changes observed during the run-in period ($P=0.03$ and $P=0.001$, respectively). Notably, the GFR reduction achieved by tolvaptan and octreotide-LAR add-on therapy exceeded the reduction achieved by tolvaptan and placebo by 3 (0–12) ml/min per 1.73 m^2 (Figure 1B), and the excess reduction was statistically significant ($P=0.01$).

Secondary Comparisons

TKV nonsignificantly decreased by 4 (−23 to 48) ml (Figure 2A) during the 1-month tolvaptan and placebo treatment period ($P=0.73$), whereas it decreased significantly by 41 (25–77) ml during the 1-month treatment period with tolvaptan and octreotide-LAR ($P<0.001$). TKV changes during the two treatment periods differed by 39.1±13.3 ml, and the difference was statistically significant ($P=0.01$). Similar results were obtained by measuring height-adjusted TKV (data not shown).

Changes in cystic kidney volume paralleled changes in TKV (Figure 2B and Supplemental Material).

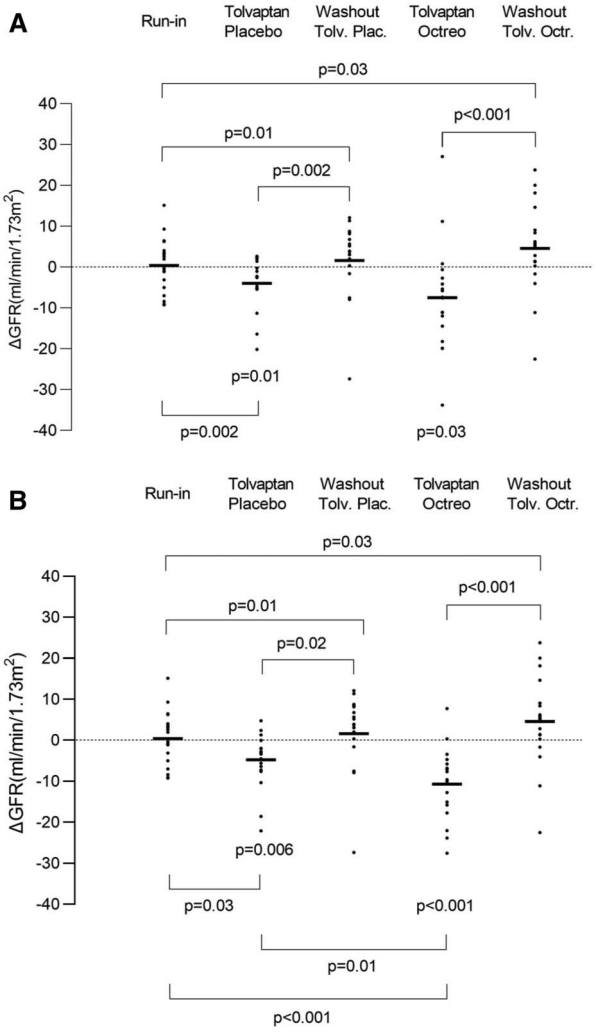

Figure 1. GFR changes during the different study periods. (A) GFR changes during the two 1-month treatment periods with tolvaptan and placebo or with tolvaptan and octreotide-LAR add-on therapy as compared with GFR changes during the run-in period and during the two corresponding washout periods from tolvaptan and placebo and from tolvaptan and octreotide-LAR. The black points indicate values of each single individual during each study period and the horizontal bars show the mean of corresponding individual points. (B) GFR changes during the two 1-week treatment periods with tolvaptan and placebo or with tolvaptan and octreotide-LAR add-on therapy as compared with GFR changes during the 1-month run-in period and during the two corresponding 1-month washout periods from tolvaptan and placebo and from tolvaptan and octreotide-LAR. The black points indicate values of each single individual during each study period and the horizontal bars show the mean of corresponding individual points. The *P* values without brackets indicate that changes observed in the considered variables in the considered period were significant. The *P* values with brackets show that the changes in the two considered treatment periods were significantly different. LAR, long-acting release; octr. and octreo, octreotide-LAR; plac., placebo; tolv., tolvaptan.

Other Exploratory Comparisons

BP data are shown in Figure 3, A and B. Heart rate significantly decreased by 5 (3–10) beats per minute ($P=0.001$) during the dual treatment period and increased significantly by 2 (0–7) beats per minute ($P=0.03$) during the subsequent washout period (Figure 3C): These opposite changes were significantly different ($P=0.003$).

Albumin fractional clearance decreased during the dual treatment period, whereas it nonsignificantly increased during the tolvaptan and placebo treatment period (Figure 3D). These two opposite changes were significantly different ($P=0.008$).

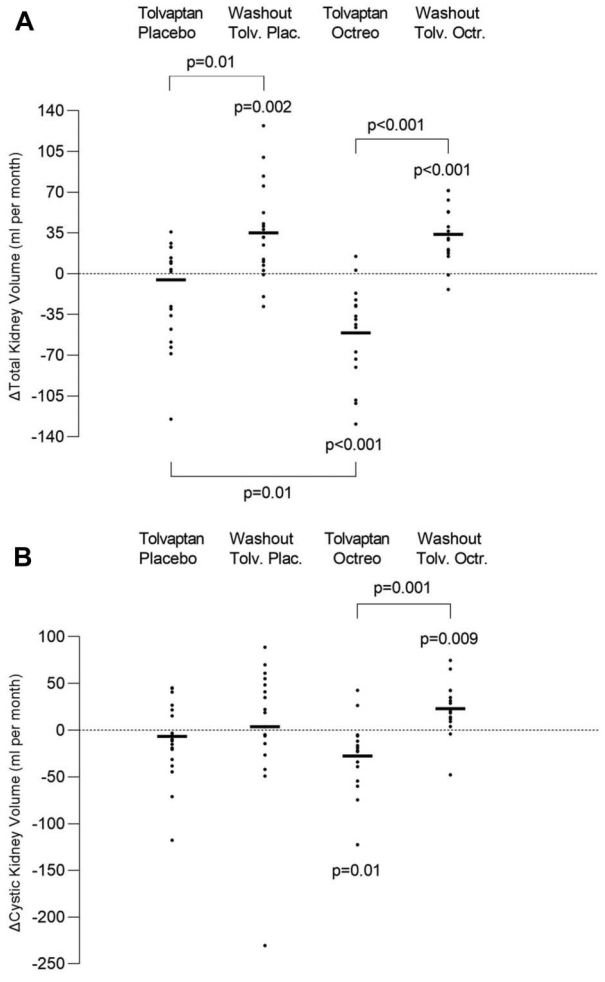

Figure 2. Changes in kidney volumes during the different study periods. Changes in total kidney volumes (A) and cystic kidney volume (B) during the two 1-month treatment periods with tolvaptan and placebo or with tolvaptan and octreotide-LAR add-on therapy as compared with changes during the two corresponding washout periods from tolvaptan and placebo and from tolvaptan and octreotide-LAR. The black points indicate values of each single individual during each study period and the horizontal bars show the mean of corresponding individual points. The *P* values without brackets indicate that changes observed in the considered variables in the considered period were significant. The *P* values with brackets show that the changes in the two considered treatment periods were significantly different.

Twenty-four-hour urinary output remarkably increased during both treatment periods ($P<0.001$ for both changes). However, the increase observed during the tolvaptan and placebo treatment period exceeded by 1193.0 (−183.0 to 1925.0) ml the increase observed during the tolvaptan and octreotide-LAR add-on therapy (Figure 4A), and the excess output was statistically significant ($P=0.02$). Changes in free-water fractional clearance paralleled those in urinary output (Figure 4B).

Changes in Physical Component Summary Score and Mental Component Summary Score during the two treatment periods were nonsignificant and did not differ between the two periods (Table 2). Changes in all other considered exploratory kidney functional parameters are reported in the Supplemental Material.

Safety

Three serious adverse events (SAEs) were reported in two patients. Increases in liver transaminases and creatine phosphokinase levels were reported as two distinct events in one patient during the dual treatment period. Both events fully recovered after tolvaptan withdrawal. The patient was maintained into the study and completed all visits. The third SAE was a SARS-CoV-2 infection that occurred during the washout period from the tolvaptan and placebo treatment period. This event was complicated by a left bundle branch block, which lead the investigator to withdraw the patient from the study. Numbers and percentages of patients with SAEs and AEs along the whole study and during each treatment period are reported in Table 3. All serious and nonserious AEs are reported in Supplemental Table 2. Notably, all AEs reported during the two treatment periods fully recovered during the corresponding washout periods. In particular, fasting morning blood glucose significantly increased with octreotide-LAR added-on tolvapan (Table 1) as compared with tolvaptan combined to placebo ($P<0.001$). However, during the whole study period, blood glucose never exceeded 125 mg/dl.

Discussion

In this pilot, prospective randomized, double blind, cross-over trial, we found that 1-week and 1-month treatment with tolvaptan and placebo significantly decreased the GFR in 19 patients with ADPKD. One-month add-on therapy with octreotide-LAR during the tolvaptan and octreotide-LAR treatment period appeared to amplify the extent of GFR reduction achieved by tolvaptan and placebo, although the additional effect on GFR failed to achieve the statistical significance. However, this significance was achieved at 1 week of treatment. One-week and 1-month GFR changes achieved during the two treatment periods were both significantly different by the GFR changes observed during the run-in period with conservative therapy only. Notably, both GFR changes were followed by two rebound GFR increases during the 1-month washout from both treatment periods. Changes in renal blood flow and renal plasma flow during the dual treatment period and during the subsequent washout period paralleled the concomitant changes in GFR. All changes were reversible and, conceivably, hemodynamic.

A comprehensive evaluation of GFR changes at 1 week and 1 month of treatment (coprimary and primary

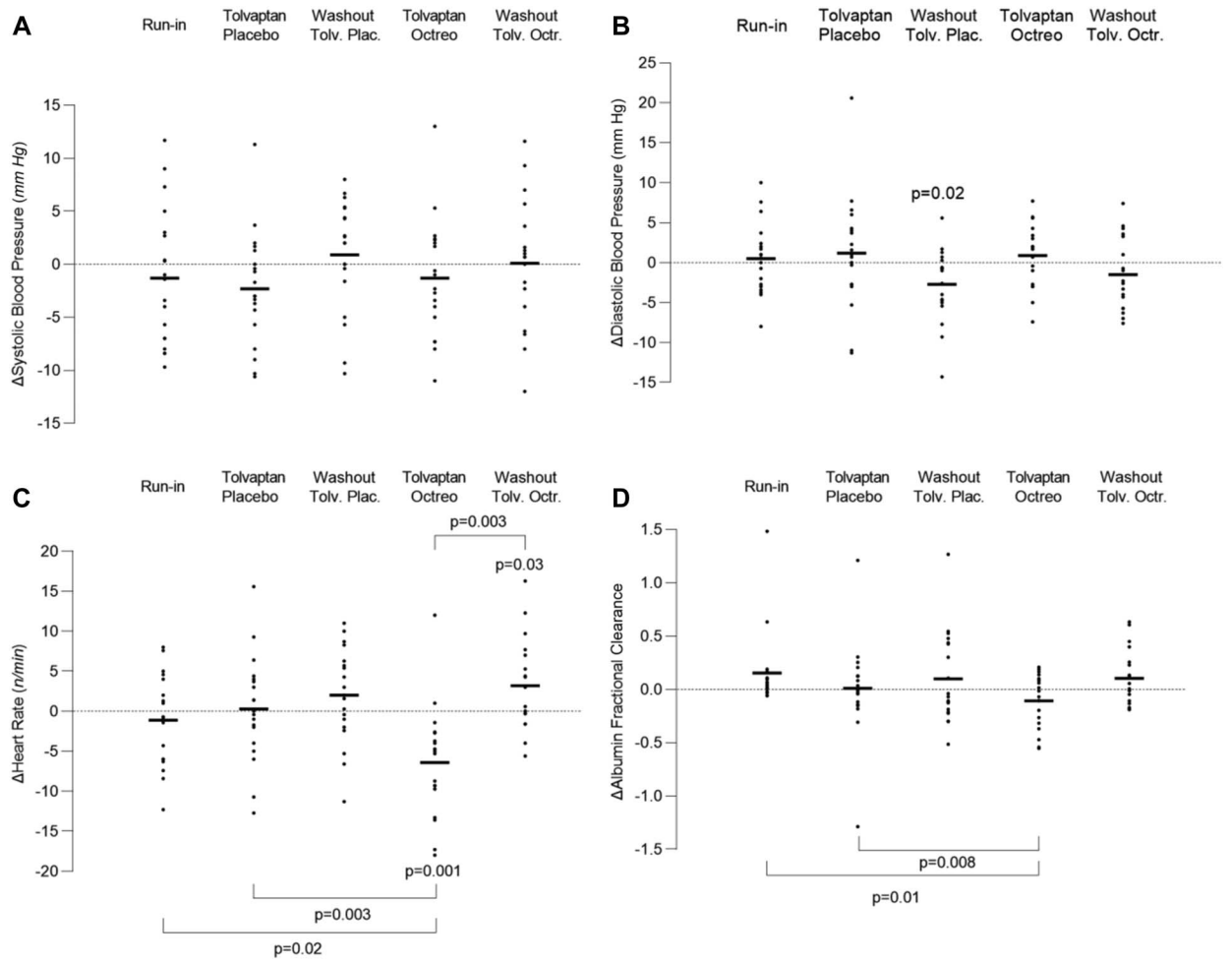

Figure 3. Changes in BP, heart rate, and albumin fractional clearance during the study periods. Changes in systolic (A) and diastolic (B) BP, heart rate (C), and albumin fractional clearance (D) during the two 1-month treatment periods with tolvaptan and placebo or with tolvaptan and octreotide-LAR add-on therapy as compared with changes during the two corresponding washout periods from tolvaptan and placebo and from tolvaptan and octreotide-LAR. The black points indicate values of each single individual during each study period and the horizontal bars show the mean of corresponding individual points. The *P* values without brackets indicate that changes observed in the considered variables in the considered period were significant. The *P* values with brackets show that the changes in the two considered treatment periods were significantly different.

outcomes of the study, respectively) appears to support the hypothesis that octreotide-LAR added-on tolvaptan therapy enhances the amelioration of single glomerular hyperfiltration achieved by tolvaptan and placebo. Notably, our patients had a total measured GFR in normal range or slightly reduced. Indeed, when the number of functioning nephrons is reduced secondarily to injuries—such growing cystic tissue in ADPKD—compensatory increase in single nephron glomerular filtration (glomerular hyperfiltration) seldom results in an increase in total kidney GFR (absolute hyperfiltration) but is just aimed to maintain total GFR in normal range or at least to limit total GFR decrease when the proportion of vital nephrons is substantially reduced (relative hyperfiltration). Further and reversible reduction of total GFR is an evidence of amelioration of this compensatory, relative hyperfiltration, amelioration that in the long term is nephroprotective.[12] Evidence that dual treatment was also associated with a significant reduction in albumin fractional clearance as compared with the tolvaptan and placebo treatment and to the run-in periods suggests that in addition to ameliorating glomerular hyperfiltration, octreotide-LAR add-on therapy could also ameliorate the glomerular barrier sieving function, an effect that is also expected to translate into long-term nephroprotection.[17] The heart rate decreased during the dual treatment period. This change that significantly differed from changes during the run-in and the tolvaptan and placebo combination therapy was most likely explained by the well-known direct cardiovascular effect of somatostatin and its analogs[18] and might hopefully be cardioprotective in the long term.[19]

Notably, TKV and cystic kidney volume were not appreciably affected by tolvaptan and placebo therapy, whereas they significantly decreased with dual therapy. The additional effect of octreotide-LAR on TKV was strong enough to achieve the statistical significance, and the additional effect on cystic kidney volume was borderline significant. As for GFR, there was a rebound TKV increase during the 1-month washout periods from

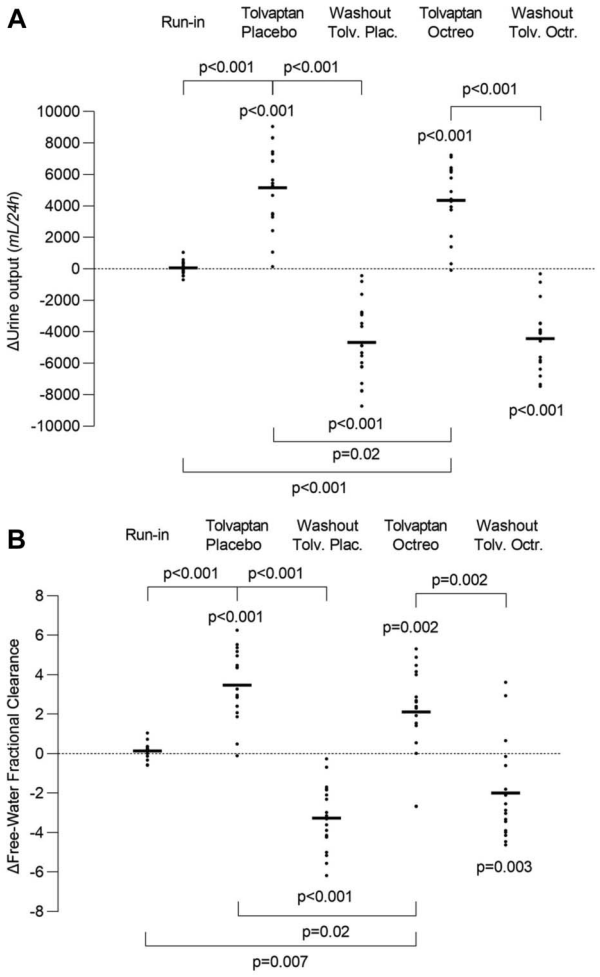

Figure 4. Changes in kidney excretory function during the different study periods. (A) Urinary output changes during the two 1-month treatment periods with tolvaptan and placebo or with tolvaptan and octreotide-LAR add-on therapy as compared with urinary output changes during the run-in period and during the two corresponding washout periods from tolvaptan and placebo and from tolvaptan and octreotide-LAR. The black points indicate values of each single individual during each study period and the horizontal bars show the mean of corresponding individual points. (B) Free-water fractional clearance changes during the two 1-week treatment periods with tolvaptan and placebo or with tolvaptan and octreotide-LAR add-on therapy as compared with free-water fractional clearance changes during the 1-month run-in period and during the two corresponding 1-month washout periods from tolvaptan and placebo and from tolvaptan and octreotide-LAR. The black points indicate values of each single individual during each study period and the horizontal bars show the mean of corresponding individual points. The *P* values without brackets indicate that changes observed in the considered variables in the considered period were significant. The *P* values with brackets show that the changes in the two considered treatment periods were significantly different.

tolvaptan and placebo and from combination therapy, whereas the cystic kidney volume rebound increase was observed only during the 1-month washout period from tolvaptan and octreotide-LAR combination therapy. Thus, the effect of tolvaptan and placebo on TKV and cystic kidney volume was negligible, and it is conceivable that the effect of dual therapy on both volumes was fully (or largely) driven by octreotide-LAR.

As previously reported with another somatostatin analog in an experimental model of polycystic kidney disease,[5] octreotide-LAR add-on therapy slightly—but significantly—reduced the diuretic effect induced by tolvaptan. Finding that diuresis reduction was associated with a parallel reduction in free-water fractional clearance suggests that the (partial) antidiuretic effect of octreotide-LAR could be mediated by a (partially) restored tubular response to the antidiuretic hormone. Thus, in combination with octreotide-LAR, tolvaptan could be better tolerated because of reduced patient discomfort related to its aquaretic properties.

There were no major safety signals throughout the whole study period. Physical and mental quality of life did not change appreciably during the two treatment periods. Virtually all patients reported symptoms related to the diuretic effect of tolvaptan. Transient and self-limited gastrointestinal symptoms were also reported after octreotide-LAR injection. All reported treatment-related side effects fully recovered during the washout periods. As expected, fasting blood glucose slightly, but significantly, increased during combined therapy as compared with tolvaptan plus placebo therapy, but blood glucose never exceeded 125 mg/dl. In actual facts, the safety profile of octreotide-LAR was remarkably superior to that of pasireotide-LAR, another somatostatin analog that induced hyperglycemia or overt diabetes in 79% or 59% of patients with ADPKD with severe polycystic liver.[20] Notably, transition from octreotide-LAR to another somatostatin analog such as lanreotide was associated with severe hyperglycemia,[21] whereas treatment with octreotide-LAR in ADPKD or any other clinical setting never caused new-onset diabetes (W. Collins. Sandostatin-LAR Investigators Brochure, 3rd ed., 2000).

The main limitation of our study was the relatively small sample size, which is characteristic of the explorative, pilot nature of the study. The number of needed study participants, however, was calculated *a priori* on the basis of the expected treatment effect of the two medications on the primary outcome and considering the pilot nature of the study. The cross-over design prevented interpatient data variability, but the 4-week washout period between the two treatment periods could not definitely rule out the possibility of a residual carry-over effect because of the small sample size. Notably, however, the observed changes in GFR during the different treatment periods were quite similar to the changes hypothesized at the time of sample size estimation, which is an indirect evidence of the robustness of the working hypothesis. Consistency of GFR changes at 1 and 4 weeks of treatment is other evidence of the robustness of the study findings. Octreotide-LAR alone in higher dose could be more effective than the combination of standard doses of octreotide-LAR added to tolvaptan because both approaches work through cAMP, and octreotide-LAR monotherapy would even avoid the side effects of tolvaptan. However, we used the 40-mg dose of octreotide-LAR to be administered every 28 days because this is the standardized and approved treatment protocol for pituitary and neuroendocrine tumors. We considered that this was the dose with the best risk/benefit profile and that higher doses of octreotide-LAR could have increased the risk of side effects without providing substantial additional benefits. On the other

Table 3. Number (%) of patients with at least one serious adverse event during the whole study period (overall) and during each treatment period considered separately

Adverse Event	Overall (*N*=19)	Run-in (*N*=19)	Tolvaptan-Placebo (*N*=19)	Washout Tolvaptan-Placebo (*N*=19)	Tolvaptan-Octreotide-LAR (*N*=18)	Washout Tolvaptan-Octreotide-LAR (*N*=18)
Any adverse event, *n* (%)	19 (100)	15 (79)	18 (95)	9 (47)	18 (100)	8 (44)
Total SAEs, *n* (%)	3 (16)	0	0	1 (5)	2 (11)	0
COVID-19	1 (5)	0	0	1 (5)	0	0
Elevated transaminase levels	1 (5)	0	0	0	1 (6)	0
Elevated CPK levels	1 (5)	0	0	0	1 (6)	0
Total nonserious AEs, *n* (%)	19 (100)	15 (79)	18 (95)	9 (47)	18 (100)	8 (44)
Left bundle branch block[a]	1 (5)	0	0	1 (5)	0	0
Polyuria[b]	19 (100)	0	17 (89)	0	18 (100)	0
Increased thirst[b]	19 (100)	0	17 (89)	0	18 (100)	0
Nocturia[b]	10 (53)	0	6 (32)	0	8 (44)	0
Flu-like syndrome[b]	9 (47)	4 (21)	4 (21)	2 (11)	0	0
Diarrhea, loose stools[b]	8 (42)	0	1 (5)	0	7 (39)	1 (6)
Abdominal pain/distension[b]	7 (26)	0	2 (11)	2 (11)	4 (22)	1 (6)
Dry mouth[b]	7 (37)	0	5 (26)	0	4 (22)	0
Light-colored stools	7 (37)	0	1 (5)	0	6 (33)	0
Tendon tear, joint, or traumatic pain[b]	6 (26)	4 (21)	2 (11)	1 (5)	0	0
Nausea/dyspepsia	6 (32)	1 (5)	2 (11)	0	3 (17)	0
Back pain/sciatica	5 (26)	1 (5)	0	0	0	4 (22)
Constipation/borborisms	5 (26)	0	3 (16)	1 (5)	1 (6)	0
Anckle edema	4 (21)	4 (21)	0	0	0	0
Headache	4 (21)	1 (5)	2 (11)	1 (5)	0	0
Fatigue	4 (21)	0	1 (5)	0	3 (17)	0
Site-injection pain	4 (21)	0	0	0	4 (22)	0
Arterial hypertension	4 (21)	3 (16)	1 (5)	0	0	0
Anemia, leukopenia, or neutropenia[b]	3 (16)	1 (5)	2 (11)	1 (5)	0	0
Dyslipidemia	3 (16)	2 (11)	1 (5)	0	0	0
Elevated CPK levels	3 (16)	1 (5)	1 (5)	0	1 (6)	0
Urinary tract infection/dysuria	3 (16)	1 (5)	0	0	0	2 (11)
Arm pain due to SARS-CoV-2 vac[b]	2 (11)	1 (5)	1 (5)	1 (5)	0	0
Acute urticaria/itching	2 (11)	0	1 (5)	0	1 (6)	0
Herpes labialis	2 (11)	1 (5)	0	0	1 (6)	0
Elevated serum uric acid levels	2 (11)	0	0	0	2 (11)	0
COVID-19	2 (11)	0	0	0	0	2 (11)
Breast nodule, breast cyst[b]	1 (5)	0	1 (5)	1 (5)	0	0
Palpitations/extrasystoles[b]	1 (5)	0	0	1 (5)	1 (6)	0
Left side numbness/tingling[b]	1 (5)	0	0	0	1 (6)	0
Pancreatic cyst	1 (5)	1 (5)	0	0	0	0
Kidney stones	1 (5)	1 (5)	0	0	0	0
Leg cramps	1 (5)	1 (5)	0	0	0	0
Hypokalemia	1 (5)	1 (5)	0	0	0	0
Sinusitis	1 (5)	1 (5)	0	0	0	0
Testicular pain	1 (5)	1 (5)	0	0	0	0
Dyspnea	1 (5)	0	1 (5)	0	0	0
Elevated LDH levels	1 (5)	0	1 (5)	0	0	0
Elevated AST levels	1 (5)	0	1 (5)	0	0	0
Menorrhagia	1 (5)	0	1 (5)	0	0	0
Microalbuminuria	1 (5)	0	1 (5)	0	0	0
Post–COVID-19 vaccination syndrome	1 (5)	0	1 (5)	0	0	0
Keratoconjuntivitis	1 (5)	0	1 (5)	0	0	0
Abdominal hematoma	1 (5)	0	1 (5)	0	0	0
Hypertensive retinopathy grade 1	1 (5)	0	0	1 (5)	0	0
Flatulence	1 (5)	0	0	0	1 (6)	0
Vomiting	1 (5)	0	0	0	1 (6)	0
Elevated serum creatinine levels	1 (5)	0	0	0	1 (6)	0
Suspected hypoglycemia	1 (5)	0	0	0	1 (6)	0
Facial numbness	1 (5)	0	0	0	1 (6)	0

LAR, long-acting release; SAEs, serious adverse events; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; AE, adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; vac, vaccine; LDH, lactate dehydrogenase; AST, aspartate aminotransferase.
[a]Discontinuation of trial because of AE.
[b]Patients have events during different treatment periods.

hand, tolvaptan is a very expensive medication with several side effects. Future studies could address whether monotherapy with higher than standard doses of octreotide-LAR would be at least as effective as standard doses of octreotide-LAR added on tolvaptan. Lack of an octreotide-LAR monotherapy arm was another limitation of the study that was explained by feasibility considerations and resource restrictions. Again, this issue could be addressed in a future study. Major strengths include the presence of a placebo arm, the excellent patient retention

despite the highly demanding design of the study, and the central measurement of GFR, kidney volumes, and kidney functional parameters by gold standard techniques which, by reducing the extent of random data fluctuation, increased the power of the analyses.

In conclusion, octreotide-LAR enhanced the beneficial effect of tolvaptan on compensatory glomerular hyperfiltration and remarkably reduced total kidney and cystic volumes in a homogeneous cohort of ADPKD patients with normal kidney function. Both medications were safe and relatively well tolerated, even in combination. Whether the present findings can be generalized to ADPKD patients with decreased GFR and whether octreotide-LAR add-on therapy may enhance the long-term nephroprotective effects of tolvaptan in patients with ADPKD is worth investigating.

Disclosures

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Author Contributions

N. Perico, G. Remuzzi, P. Ruggenenti, and M. Trillini conceptualized the study; P. Brambilla, A. Caroli, F. Carrara, D. Cugini, D. Martinetti, A. Remuzzi, P. Ruggenenti, and G. Villa were responsible for data curation and visualization; P. Brambilla, A. Caroli, T. Peracchi, A. Perna, N. Rubis, P. Ruggenenti, A. Remuzzi, G. Remuzzi, and M. Trillini were responsible for formal analysis, project administration, software, and validation; P. Ruggenenti and M. Trillini wrote the original draft; G. Remuzzi and P. Ruggenenti were responsible for funding acquisition and resources; N. Perico and N. Rubis provided supervision; P. Brambilla, A. Caroli, F. Carrara, D. Cugini, and A. Remuzzi were responsible for methodology; A. Caroli, M.R. Caruso, V. Leone, M. Trillini, and G. Villa were responsible for investigation; and all authors reviewed and edited the manuscript.

Data Sharing Statement

Sharing of individual participant data with third parties was not specifically included in the informed consent of the study, and unrestricted diffusion of such data may pose a potential threat of revealing participants' identities, as permanent data anonymization was not carried out. To minimize this risk, individual participant data that underlie the results reported in this article will be available after 3 months and up to 5 years from article publication. Researchers shall submit a methodologically sound proposal to renemedbiostatistics@marionegri.it. To gain access to data, requestors will need to sign a data access agreement and obtain approval of the local ethics committee.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B565.

Supplemental Methods.

Supplemental Results.

Supplemental Figure 1. Study design.

Supplemental Figure 2. Study flow chart.

Supplemental Table 1. Number (%) of patients with concomitant medications at baseline in the study group considered as a whole (overall) and according to the randomization to the two sequences of treatment with octreotide-LAR followed by placebo or with placebo followed by octreotide-LAR, both on top of tolvaptan.

Supplemental Table 2. Total number of serious AEs and nonserious AEs throughout the whole study period (overall) and during each period considered separately.

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See related editorial, "Concurrent Targeting of Vasopressin Receptor 2 and Somatostatin Receptors in Autosomal Dominant Polycystic Kidney Disease: A Promising Approach for Autosomal Dominant Polycystic Kidney Disease Treatment?" on pages 154–156.