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RESEARCH ARTICLE

Octreotide LAR in Patients with Autosomal Dominant Polycystic Kidney Disease: From Bench to a Novel Perspective of Therapy

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ABSTRACT

Polycystins 1 or 2 congenital defects result in impaired Ca^{2+} inflow through the tubular cell membrane with reduced intracellular Ca^{2+} concentration and secondary adenylcyclase over-activation with increased intracellular cAMP. This activates chloride-driven fluid secretion and tubular cell proliferation and de-differentiation with cyst formation and growth. Thus, medications, such as the somatostatin analogue Octreotide LAR or the vasopressin antagonist Tolvaptan, that reduce intracellular cAMP, have been tested to inhibit cAMP-mediated chloride secretion and cell proliferation in experimental and human polycystic kidney disease. Seminal studies conducted in the early '80s by Franklin Epstein showed that in the shark rectal gland chloride secretion is markedly inhibited by somatostatin in a way suggesting inhibition of adenylcyclase. Evidence that specific receptors for somatostatin, in particular the sst2 subtype, are present in tubular cell membranes suggested that Octreotide LAR binding to its specific renal receptors could exert similar effects in ADPKD cells. In a pilot, cross-over safety study we found that 6-month Octreotide LAR therapy was safe and well tolerated in 12 patients with ADPKD and significantly decreased total kidney volume growth as compared to placebo. Then, the ALADIN and ALADIN II academic, prospective, randomized, placebo-controlled clinical trials found that 3-year Octreotide LAR treatment significantly slowed total kidney and cyst volume growth. In ALADIN treatment slowed chronic decline of directly measured GFR in 79 patients with estimated GFR ≥ 40 ml/min/1.73 m^2. In ALADIN II treatment slowed progression to doubling of serum creatinine or ESKD in 100 patients with stage 3b-4 CKD. Treatment was equally safe and well tolerated in both studies. Sub-studies also showed that 3-year Octreotide LAR therapy reduced total liver volume in 27 ADPKD patients with associated polycystic livers and improved left ventricular twisting and untwisting function in 34 ADPKD patients assessed by speckled-tracked echocardiography. Future trials should confirm the long-term benefits of Octreotide LAR in larger populations of ADPKD patients. Moreover, recent studies found that somatostatin analogues and Tolvaptan have additional beneficial effects in experimental polycystic kidney disease. Thus, clinical trials should also explore whether Octreotide LAR and Tolvaptan in combined therapy may have an additional beneficial effect even in human disease.

The Epidemiology and Outcome of ADPKD as an "Orphan Disease"

The relatively "rare" Autosomal-dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, responsible for 8% to 10% of end-stage kidney disease (ESKD) cases in Western countries.[1] ADPKD is genetically heterogeneous, with at least three different genes implicated: the *PKD1* and *PKD2* genes involved in approximately 85% and 15% of the cases, respectively and a *PKD3* gene not yet identified.

PKD1 is associated with a more severe condition with an average age of ESKD at about 54 years compared to 73 years for PKD2 cases.[1] Moreover, patients with ADPKD have a faster decline in glomerular filtration rate (GFR) than patients with other renal diseases, at comparable levels of blood pressure control and proteinuria, and do not seem to benefit to the same extent from angiotensin-converting enzyme (ACE) inhibitor therapy.[2–6] A reasonable explanation for these findings is that progression in ADPKD is largely related to disease-specific mechanisms such as the development and growth of cysts and concomitant disruption of normal renal tissue, whereas arterial hypertension surely has a minor relative role and proteinuria, the strongest determinant of CKD progression, is usually absent or present in small amounts only in latest stages of the disease.[7] Thus, ACE inhibitors and the more recent inhibitors of the renin angiotensin system (RAS) angiotensin receptor blockers (ARBs) are particularly poorly effective[5,6] largely because these medications exert large part of their nephroprotective effect in proteinuric nephropathies by restoring the physiological sieving function of the glomerular barrier that in proteinuric chronic kidney diseases is lost and allows large amounts of plasma proteins to be ultrafiltered in excess and exert their nephrotoxic effect at glomerular and tubulo-interstitial level.[8] But, at least in early stages of the disease, glomerular sieving function is preserved in patients with ADPKD and therefore the nephroprotective effects of RAS inhibitors in this context is negligible because they interfere with a pathophysiological mechanism that has a marginal role in the progression of the disease. Thus, renal protective interventions in ADPKD, more than addressing arterial blood pressure and proteinuria, and limiting the effects of other potential promoters of disease progression such as dyslipidemia chronic hyperglycemia smoking, should be specifically aimed to correct the dysregulation of epithelial cell growth, secretion, and matrix deposition that is characteristic of the disease.[7] This explains why, before "disease modifiers" such as the vasopressin antagonist Tolvaptan and the Somatostatin analogue Octreotide Long Acting Release (LAR) became available for clinical use, approximately 50% of ADPKD patients treated with conservative therapy only required renal replacement therapy by 60 years of age.[9] On this regard, however, it is important to note that in recent years extremely effective nephroprotective medications such as Sodium-Glucose-Cotransporter-2 (SGLT2) inhibitors, dapagliflozin, empagliflozin and canagliflozin have become available. These medications have been proven to be particularly nephroprotective in CKD stages 3 to 4 (and cardioprotective in earlier stages) and even in non-proteinuric forms of CKD.[10] These medications, however, have never been tested in patients with ADPKD because of concern for specific side effects emerged from basic studies in experimental models of polycystic kidney disease.[11,12] This is an issue that would merit further investigation.

The Paradigmatic Case of an ADPKD Patient on Chronic Octreotide LAR Therapy for a Secreting Adenoma of the Pituitary Gland

Our research program on the effects of Octreotide LAR in ADPKD stemmed from a close cooperation with Franklin H Epstein[13] who from the early '80s was investigating mechanisms of somatostatin-modulated sodium chloride secretion from the shark rectal gland[14,15] Notably, at that time we were faced with the surprising experience of an ADPKD female patient who was on chronic treatment with Octreotide LAR for the inhibition of uncontrolled growth hormone secretion from an adenoma of the pituitary gland. A comparative analysis of two computed tomography (CT) scans taken at the time Octreotide LAR treatment was started (A) and 2 years later (B) failed to detect any appreciable change in kidney and kidney cyst volumes (Figure 1).[16] This finding, combined with the stable kidney function observed during the same observation period, suggested a possible role of Octreotide LAR in the inhibition of the growth of renal cysts that might have prevented further damage to the residual functioning kidney parenchyma.[16] Evidence that from a revision of abdominal CT scan images of ADPKD recorded at our ADPKD-CT data base no other case of patient on conservative therapy only showed stabilization or even shrinkage of kidney cysts over such a long observation period, corroborated the working hypothesis of a specific nephroprotective effect of Octreotide LAR in ADPKD.

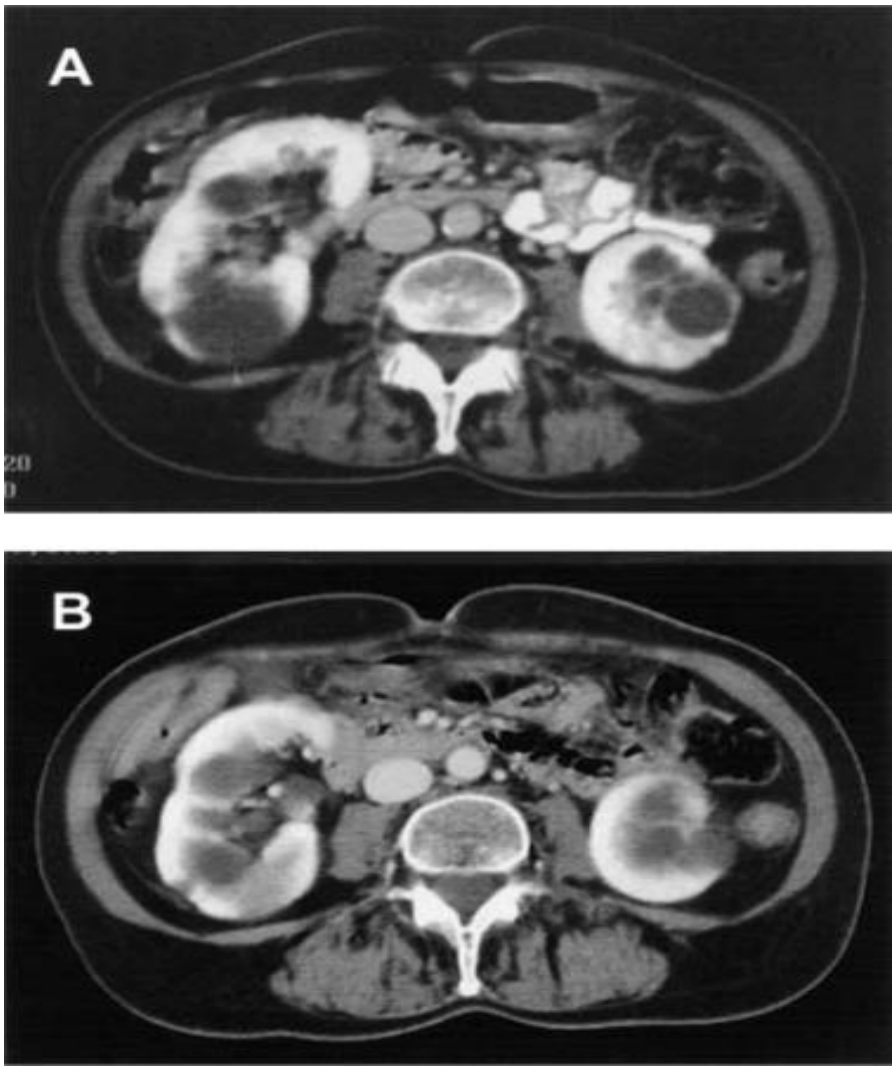

Figure 1: Representative images of abdominal computed tomography (CT) scan of a patient with ADPKD before (A) and after (B) 2-year treatment with the somatostatin analogue Octreotide LAR for an adenoma of the pituitary gland. No appreciable differences in kidney and kidney cysts diameters can be observed between the two scans

Understanding Disease Mechanisms to Identify Disease-Modifying Interventions: From Bench to the Clinics

The fluid filling renal cysts in human polycystic kidneys, as well as in many forms of experimental cystic disease in rats, is formed chiefly by a process of secretion by the tubular epithelium lining the cysts.[17,18] Secretion and reabsorption take place at approximately the same rate, with secretion slightly exceeding reabsorption, so that the amount of fluid in the cysts increases slowly over time. This process of active secretion, via the molecular mechanism of secondary active chloride transport,[19] is also responsible for secretion of fluid into the lumen by proximal renal tubules in teleost and elasmobranch fishes[20,21] and in the rectal (salt-excreting) gland of elasmobranchs.[22] In kidney tubular cells, this sequence of events is modulated by Polycystin1 (PC1) and Polycystin2 (PC2) that are located in the primary cilium and modulate extracellular Ca^{2+} inflow in response to a series of extracellular mechanical or chemical stimuli.[23] Mutations in one of the genes encoding for one of the two Polycystins (PC1 or PC2) may result in dysfunction of this "Ca^{2+} channel", with impaired Ca^{2+} inflow and reduced intracellular Ca^{2+} concentration (Figure 2, Left Panel). Through several mechanisms, $[Ca^{2+}]$ reduction may result in adenylcyclase over-activation with increased intracellular cAMP and consequent activation of Cl^- driven fluid secretion and cell cycle activation with consequent tubular cell proliferation and de-differentiation (Figure 2, Left Panel) with uncontrolled cyst formation and growth. Thus, lowering intracellular cAMP levels - in order to inhibit chloride secretion and cell proliferation - has become a major focus in the development of interventions to treat ADPKD patients.[24,25] In this perspective, the seminal studies conducted in the

early '80s by Prof. Franklin Epstein at Mont Desert Island Laboratory (Maine, USA) had shown that in the shark rectal gland chloride secretion is markedly inhibited by somatostatin in a way suggesting inhibition of adenylcyclase[14,15] Evidence that specific receptors for somatostatin are present in human kidneys,[26] suggests the possibility that somatostatin might interact with somatostatin-specific receptors located on tubular cells membranes and corroborates the hypothesis that Octreotide treatment of ADPKD patients might inhibit fluid formation and eventually induce shrinking of renal cysts by interacting with these receptors, in particular with the sst2 receptor (see below) (Figure 2 Right Panel).

Somatostatin is a cyclic 14 aminoacid peptide secreted by pancreatic islets (D cells), gastrointestinal tract, nervous system, and thyroid gland.[27] There are two native biologically active forms of somatostatin, and a number of synthetic analogues have been described.[28] Genes for five somatostatin receptor subtypes have been cloned and are named sst1 to sst5. All receptors bind molecular forms of somatostatin as well as somatostatin analogues with varying affinity for the agonists. The sst2 receptor is the most frequently present in kidney tissue, and shows a high affinity for the somatostatin analogue Octreotide.[26] Effector systems of sst2 receptors are inhibitors of adenylate cyclase and stimulators of phosphatase and phospholipase C.[27] Up to September 2004, several somatostatin analogues had become available for clinical use and have been used with negligible side effects for long-term treatment (up to 8 to 12 months) of multiple endocrine tumors.[29] Thus, on the basis of the aforementioned basic research findings,[15] occasional clinical observations[16] and encouraging safety evidence in other clinical settings (adenomas of the pituitary gland and some neuroendocrine tumors),[29] we decided to design and conduct a fully independent, academic, pilot study to primarily assess the safety-profile and secondarily the renal structural and functional effects of the long-acting-release (LAR) somatostatin analogue Octreotide LAR in patients with ADPKD and varying degrees of renal dysfunction.

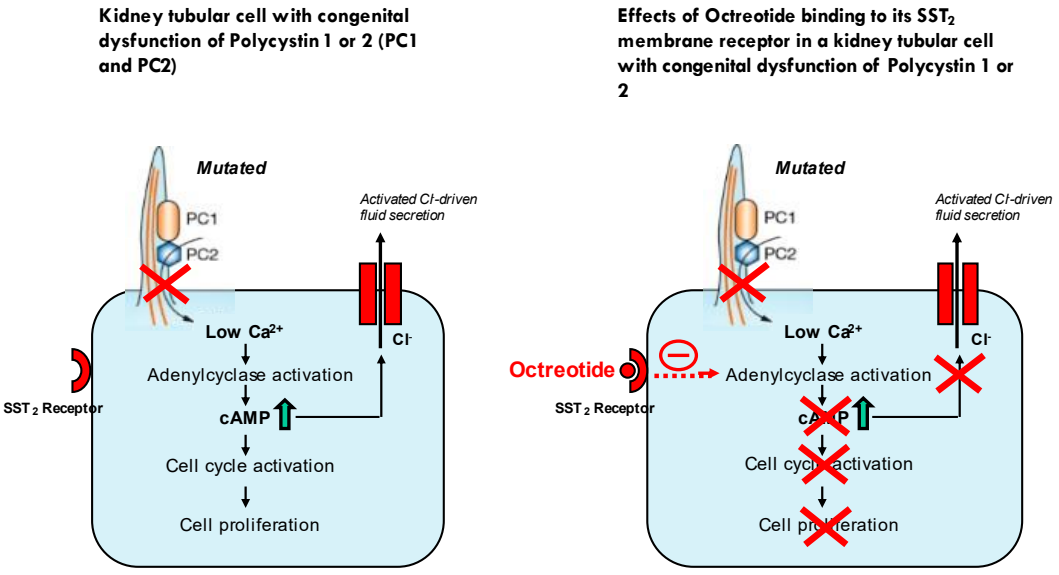

Figure 2: Mechanisms in Ca^{2+} -modulated cAMP-mediated Cl^- secretion and kidney proliferation at kidney tubular cell and inhibitory effects of somatostatin (or somatostatin analogues) on cAMP production and activity. Intrinsic abnormalities in genes encoding for Polycystin 1 (PC1) and Polycystin 2 (PC2) located on tubular cell primary cilium result in decreased Ca^{2+} inflow with consequent adenylcyclase activation with increased cAMP production and activity (Left Panel). This stimulates Cl^- extracellular secretion and cell cycle activation with cell proliferation. Somatostatin (or somatostatin analogues such as Octreotide LAR), through interaction with a specific sst_2 receptor on tubular cell surface, inhibits adenylcyclase activity with secondary reduction of Cl^- extracellular secretion and cell cycle activation with cell proliferation (Right Panel).

A Pilot, Safety, Randomized, Cross-over Trial with Exploratory Efficacy Outcomes

This pilot, randomized, longitudinal, cross-over study compared the safety and efficacy of 6-month treatment with Octreotide LAR or placebo in adult patients with ADPKD.[16] The safety and tolerability of Octreotide LAR were assessed by comparing the incidence of serious and non-serious adverse events as well as of clinically relevant changes in several laboratory parameters throughout both treatment periods. The efficacy profile was assessed by comparing the effects of the two study treatments on kidney structure and functional determinations. The main efficacy variable was total kidney volume. Secondary efficacy variables were cystic and parenchyma volumes (that is: non-cystic kidney volume), determined by spiral CT scan evaluations, and GFR, as determined by the iohexol plasma clearance technique,[30] recorded at baseline and at the end of each treatment period. We also evaluated the morpho-functional relations between concomitant changes in kidney volumes and GFR. Eligible patients provided written informed consent to study participation. No registration number is available because the study was ideated in the late '90s and published in 2005, that is largely before October 2013 when the 64th World Medical Association General Assembly established that "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject." (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ accessed on September 9, 2022)

PATIENT SELECTION - Patients aged 18 years or older, with a clinical and echographic diagnosis of ADPKD and a serum creatinine concentration >1.2 mg/dL (males) or >1.0 mg/dL (females) but <3.0 mg/dL, were selected for study participation. Exclusion criteria have been detailed elsewhere.[16]

STUDY DESIGN - At a screening visit, potentially eligible patients had an ultrasound evaluation of the kidneys and liver to rule out urinary tract or gallbladder lithiasis. Blood pressure was measured with a standard sphygmomanometer. Blood and urine samples were taken in the morning with the patient fasting for routine laboratory evaluations. The GFR was measured by the iohexol plasma clearance technique.[30] Parenchymal resistive indexes of both kidneys were evaluated by Doppler ultrasounds. Total kidney, cysts, and parenchymal volume were evaluated by spiral CT and morphometric analysis as described in detail in the *Supplementary Material*.

After baseline evaluations, patients were randomly allocated to start a 6-month treatment period with 40 mg of Octreotide LAR (Sandostatin LAR® Depot; Novartis Pharma AG, Basel, Switzerland) intramuscularly injected every 28 days (two intra-gluteal 20 mg injections) or placebo (saline added with B12 vitamin) injected with the same identical procedures. Every 2 months blood pressure, routine laboratory tests and a kidney and liver ultrasound were evaluated. At 6 months, all baseline evaluations were rerun. Then, patients crossed over to the other treatment arm and measurements performed during the first treatment period were repeated every 2 months and at completion of the second treatment period.

BASELINE PATIENT CHARACTERISTICS - Fourteen patients entered the study. Their pre and post treatment clinical and laboratory parameters are shown in Table 1. Additional information is presented in the *Supplementary Material*.

SAFETY AND TOLERABILITY – We found that in adult patients with ADPKD and different degrees of renal dysfunction 6-month treatment with Octreotide LAR was safe and well tolerated. Only one patient had to interrupt Octreotide therapy prematurely because of asymptomatic cholelithiasis that disappeared after a few months of treatment with ursodeoxycholic acid.[31] No significant changes in laboratory parameters were observed during Octreotide LAR. In particular, in the study group as a whole there were no significant changes in blood glucose and hemoglobin A_{1c} (HbA_{1c}) levels. These reassuring findings are consistent with previous evidence that chronic treatment with Octreotide LAR only occasionally increased fasting blood glucose and HbA_{1c}, or reduced glucose tolerance, but never caused new onset diabetes in other clinical settings (W. Collins. Sandostatin® LAR® Investigators Brochure, 3rd ed., 2000). This is in striking and concerning contrast with finding that Pasireotide LAR induced hyperglycemia in 26 of 33 treated ADPKD patients (79%) [as compared to only four controls of the 15 ADPKD patients (27%) on placebo] and overt diabetes in 19 patients (59%) [versus only 1 case in the control group (7%, $p<0.0001$)][32] – These findings in ADPKD patients are consistent with clear evidence that hyperglycemia and overt diabetes are established and relatively frequent serious side effects of Pasireotide in other typologies of patients.[33]

Table 1. Main clinical and laboratory parameters of participants of the Pilot Study at start and end of each treatment period with Placebo or Octreotide LAR.

		Placebo		Octreotide LAR	
		Start	**End**	**Start**	**End**
Systolic blood pressure	*(mmHg)*	143 ± 12	143±9	141±8	143 ± 13
Diastolic blood pressure	*(mmHg)*	94 ± 12	91±9	91±12	94 ± 14
Creatinine	*(mg/dl)*	1.8 ± 0.9	2.1±1.0	2.1±1.1	2.2 ± 1.1
Creatinine clearance	*(ml/min/1.73 m²)*	54.9 ± 21.9	52.4±25.0	56.7±29.1	53.5 ± 28.9
Aspartate aminotransferase (AST)	*(U/L)*	21.9 ± 6.2	22.5±7.6	23.6±5.6	25.0 ± 5.6
Alanine aminotransferase (ALT)	*(U/L)*	23.5 ± 7.7	25.0±11.8	30.2±13.4	29.1 ± 13.8
Gamma glutaryl transaminase (GGT)	*(U/L)*	17.3 ± 13.8	21.0±14.5	19.5±14.6	19.0 ± 15.2
Biliary acid	*(mmol/L)*	3.3 ± 1.8	3.4±1.3	4.1±1.8	4.2 ± 1.9
Alkalyne Phosphatase	*(U/L)*	60.8 ± 17.5	63.0±19.4	62.5±18.2	61.9 ± 18.8
Activated partial thrombo-plastine time (APTT) ratio		1.1 ± 0.1	1.0±0.1	1.0±0.1	1.0 ± 0.1
Prothrombin time (PT) INR		1.0 ± 0.0	1.0±0.0	1.0±0.1	1.0 ± 0.1
Calcium	*(mg/dl)*	9.1 ± 0.3	9.2±0.2	8.6±1.7	8.6 ± 1.7
Phosphorus	*(mg/dl)*	3.6 ± 0.7	3.7±0.7	3.7±0.8	3.6 ± 0.7
Sodium	*(mEq/L)*	141.5 ± 2.1	142.1±2.1	141.8±2.5	142.2 ± 1.7
Potassium	*(mEq/L)*	4.4 ± 0.4	4.3±0.3	4.4±0.4	4.4 ± 0.4
Blood glucose	*(mg/dl)*	93.9 ± 12.0	93.5±14.0	100.0±16.0	102.8 ± 14.9
Uric acid	*(mg/dl)*	6.7 ± 1.6	6.9±1.3	7.2±1.8	7.3 ± 1.8

Data are mean ± SD.

KIDNEY VOLUMES - Total kidney, cystic and parenchymal volumes before and after treatment with Octreotide LAR or placebo are shown in Table 2 (along with other kidney functional parameters). Individual absolute and relative total kidney volume changes during the two treatment periods are shown in Figure 3. On average, the volume of both kidneys significantly increased by 71 ± 107 mL ($P < 0.05$) during Octreotide LAR treatment and by 162 ± 114 mL ($P < 0.01$) during placebo (Table 2). Thus, on Octreotide LAR the volume increase was about 60% less than on placebo. Total volume increase during placebo treatment was mainly due to a significant increase in the volume occupied by renal cysts (106 ± 105 mL) ($p < 0.01$) and was only marginally influenced by concomitant changes in the "parenchymal" volume, which increased by only 9 ± 22 mL (Table 2). The increase in kidney volume during treatment with Octreotide LAR was entirely due to the concomitant increase in the volume identified as renal cysts (61 ± 106 mL), since the "parenchymal" volume actually numerically decreased by 10 ± 24 mL (Table 2).

As shown in Figure 3 (Right Panel), on Octreotide LAR treatment the percent increase in total kidney volume was significantly lower than on placebo (2.2 ± 3.7% vs. 5.9 ± 5.4%, respectively) ($P < 0.05$). This difference was the result of a numerically lower growth of cyst volume on Octreotide LAR than on placebo (3.0 ± 6.5% vs. 5.6 ± 5.8%) and of opposite changes in "parenchymal volume," that non-significantly decreased by 4.4 ± 8.9% on Octreotide LAR, but actually increased by 2.5 ± 8.4%, on placebo.

RENAL FUNCTION - As shown in Table 2, GFR decreased by approximately 9%, from 59.5 ± 25.2 to 54.0 ± 23.6 ml/min/1.73 m², in only six months of Octreotide LAR treatment, whereas it showed no appreciable change during placebo therapy. Other variables did not change appreciably (Table 2).

Table 2. Kidney functional and structural parameters in patients included in the Pilot study before and after 6-month treatment with placebo or Octreotide LAR

	Placebo		Octreotide LAR	
	Before	After	Before	After
Serum creatinine *mg/dL*	2.0 ± 1.0	2.2 ± 1.1	1.9 ± 0.8	2.1 ± 1.1
Diuresis *mL/24 hours*	1954 ± 599	2054 ± 590	1979 ± 530	2046 ± 667
Glomerular filtration rate *mL/min/1.73 m²*	**57.9 ± 22.4**	**57.7 ± 25.7**	**59.5 ± 25.2**	**54.0 ± 23.6**
Urinary albumin excretion *µg/min*	33 (9-543)	49 (8-595)	31 (13-437)	42 (7-543)
Resistive index, left	0.61 ± 0.07	0.64 ± 0.08	0.61 ± 0.08	0.64 ± 0.05
Resistive index, right	0.64 ± 0.06	0.65 ± 0.06	0.63 ± 0.07	0.66 ± 0.07
Total kidney volume *mL*	2461 ± 959	2623 ± 1021[a]	2551 ± 1053	2622 ± 1111[b]
Cyst volume *mL*	1656 ± 826	1762 ± 882	1709 ± 908	1770 ± 941
Parenchymal volume *mL*	242 ± 62	251 ± 72	247 ± 67	237 ± 65
Residual volume *mL*	562 ± 280	609 ± 325	595 ± 323	615 ± 347

Data are mean ± SD or median and (range). Student *t* test for paired data. a: $p < 0.05$; b: $p < 0.01$ vs. start.

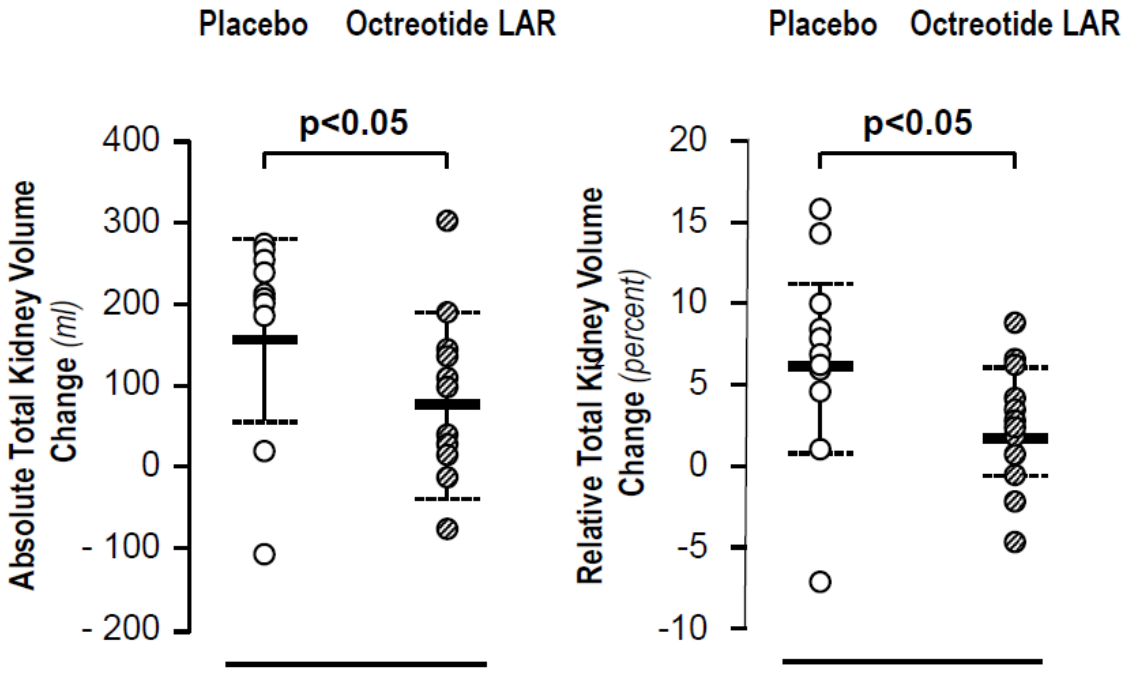

Figure 3: Average (SEM) and individual absolute (Left Panel) and percent (Right Panel) changes in total kidney volume, in the whole study group at the end of placebo and Octreotide LAR treatment along with changes in individual patients considered separately (white or dashed circles). Student *t* test for paired data.

From a Pilot, Safety Study to two Prospective, Randomized, Placebo-Controlled Clinical Trials in ADPKD Patients with a Wide Spectrum of Kidney Dysfunction from Early to Late Stage CKD

In addition to confirm the remarkably good safety profile and tolerability of Octreotide LAR and to provide the fully novel information that Octreotide LAR retards the time-dependent increase in total kidney volume, our pilot study found that the GFR tended to decrease on Octreotide LAR by approximately 9%. This finding might have major clinical implications because this effect could reflect an Octreotide-induced amelioration of compensatory hyperfiltration, a pathophysiological response of surviving and relatively "healthy" nephrons to nephron damage caused by

uncontrolled cystic growth resulting in progressive nephron mass reduction and worsening kidney dysfunction.[34] Conceivably, amelioration of this maladaptive compensatory mechanism might prove nephroprotective in the long term.[34]

The reassuring safety profile of the drug (even in other clinical settings including the treatment of secreting adenomas of the pituitary gland or some neuroendocrinal tumors), and the preliminary evidence of efficacy in ADPKD patients provided a robust background to design two randomized clinical trials to test the nephroprotective effects of Octreotide LAR in patients with ADPKD and (relatively) preserved (ALADIN) or severely impaired (ALADIN II) kidney function.

Slowing Kidney and Cyst Growth and Progressive Renal Function Decline in Patients with Early Stage ADPKD: The ALADIN Trial

The "Effect of A Long-Acting somatostatin on DIsease progression in Nephropathy due to autosomal dominant polycystic kidney disease (ALADIN)" is a prospective, randomized, multicenter, placebo-controlled clinical trial aimed to assess the effect of 3 years of Octreotide LAR treatment on kidney and cyst growth and renal function decline in 79 ADPKD participants with normal renal function or mild-to-moderate renal insufficiency (Clinical trial gov: NCT00309283).[35]

We found that 3-year treatment with Octreotide LAR slowed total kidney and cyst growth without appreciable effects on non-cystic volume. Total kidney volume (TKV) and total cystic volume (TCV) at baseline and their changes at follow-up were significantly correlated. Throughout the whole study period, the annual rate growth in total kidney volume, height-adjusted kidney volume and total cyst volume significantly and consistently declined with Octreotide LAR as compared to placebo, whereas non-cystic volume changes were not appreciably affected in any of the two treatment groups (Figure 4). The GFR similarly decreased in the two treatment groups during the first year of follow-up. Thereafter, however, the GFR stabilized in the Octreotide LAR group, whereas it continued to relentlessly decline in the placebo group (Figure 5, Left Panel); thus, following the first year, the difference in the rate of chronic renal function loss (chronic GFR decline) was significantly different between groups (Figure 5, Right Panel). Notably, in the Octreotide LAR group, initial short-term GFR reduction was inversely correlated with subsequent chronic GFR decline, thus participants with the largest initial reductions were those who were more effectively protected from progressive renal function loss in the long-term. This finding was consistent with the hypothesis that early amelioration of compensatory glomerular hyperfiltration results in effective protection against accelerated nephrosclerosis and kidney failure. Treatment was safe and well tolerated in all participants.

Consistent with previous findings in ADPKD patients receiving long-term treatment with the V_2 receptor antagonist Tolvaptan,[36] the protective effect of Octreotide LAR against TKV growth was larger in the first year of treatment than at subsequent follow-up. Conceivably, fluid secretion into cysts might acutely decrease shortly after initiation of Octreotide LAR treatment, and then stabilize 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 ADPKD patients, a 3–4% reduction in TKV was noted within 1–3 weeks of treatment with Tolvaptan,[37] a drug shown to share with somatostatin a similar inhibitory effect on cAMP-mediated cyst-cell fluid secretion in vitro.[25] Notably, even in our pilot study[16] Octreotide LAR was observed to decrease acutely by 9% the GFR during just six months of treatment, whereas no appreciable change in GFR was observed in patients on placebo. Somatostatin is known to acutely decrease GFR in healthy individuals,[38] and in patients with type 1 diabetes[39] or liver cirrhosis[40] by hemodynamic mechanisms that are probably mediated by inhibited growth hormone secretion and action.[41] Thus, in ADPKD patients this effect might contribute to blunt the compensatory hyperfiltration of glomeruli surviving the disruptive effects of uncontrolled cyst growth.[42] 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, events that almost invariably accompany the course of ADPKD, in particular in the most advanced stages characterized by accelerated renal function loss.[43] 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.[34]

Consistent with previous reports, biliary tract disease seemed to be the most clinically relevant complication related to treatment (Table 3).[44] However, it was asymptomatic in most cases and never needed treatment withdrawal. Diarrhea, 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. Self-limiting hypoglycemic 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. No patient developed hyperglycemia or overt diabetes. Thus, we can reasonably conclude that in ADPKD patients with well-preserved kidney function Octreotide LAR is safe and well tolerated.

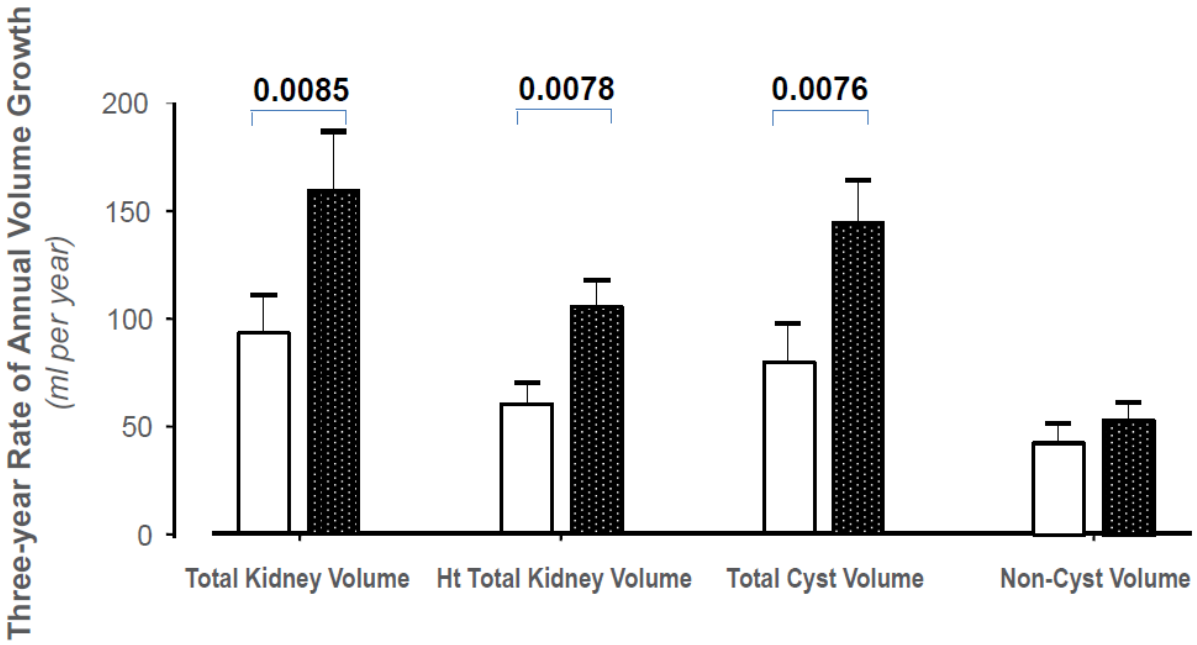

Figure 4: Total kidney volume (TKV), height adjusted total kidney volume (HtTKV), total cyst volume (TCV) and non-cyst volume (NCV) 3-year annual slopes in patients of the ALADIN trial on Octreotide LAR (white columns) or Placebo (Black columns) from baseline to study end. All considered slopes were significantly slower with Octreotide LAR than with placebo, with the only exception of non-cyst volume slopes that did not differ appreciably between treatment groups.

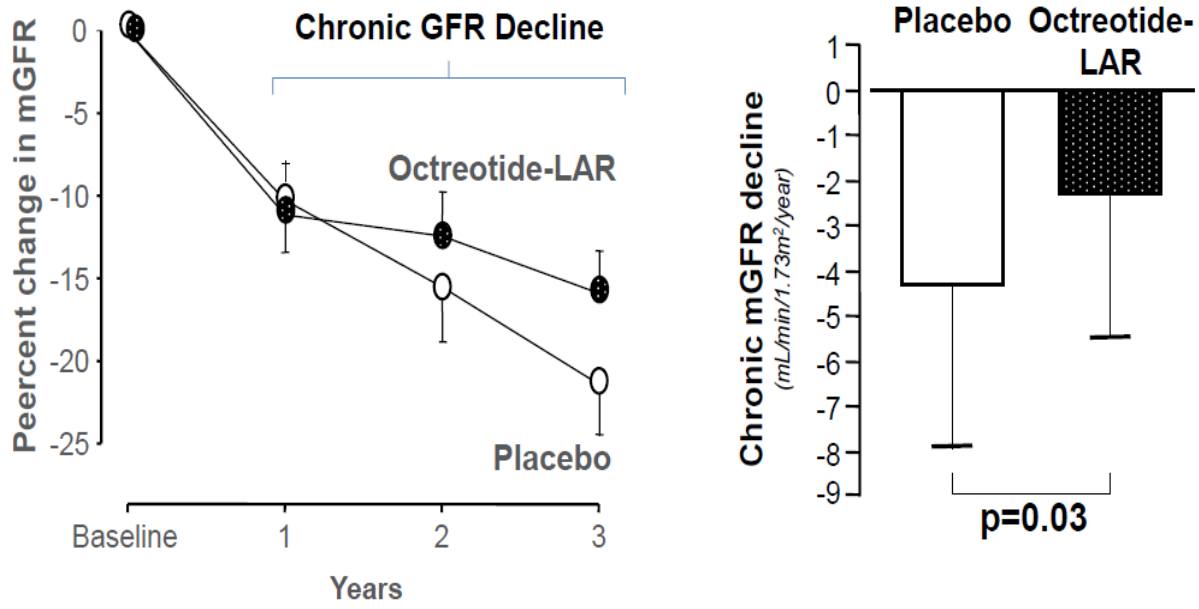

Figure 5: Percent changes in measured GFR at 1, 2 and 3 years of follow up versus baseline (Left Panel) and rate of chronic GFR decline from 1 to 3 years after randomization (Right Panel) in patients on Octreotide LAR or placebo of the ALADIN trial. From year 1 to year 3 chronic measured GFR decline was significantly slower in patients on Octreotide LAR than in controls on placebo.

Table 3. Patients from ALADIN and ALADIN II with at least one serious adverse event in the Octreotide LAR and in the Placebo groups considered separately.

	ALADIN		ALADIN2	
	Octreotide LAR *(n= 40)*	**Placebo** *(n=39)*	**Octreotide LAR** *(n= 51)*	**Placebo** *(n=49)*
Overall	**6 (15.0)**	**7 (18.0)**	**12 (23.5)**	**11 (22.4)**
Acute renal failure	0	0	2 (3.9)	2 (4.1)
Cyst infection or rupture or infection	0	0	1 (2.0)	3 (6.1)
Urinary tract infection	2 (5.0)	1 (2.6)	0	1 (2.0)
Sepsis	1 (2.5)	2 (5.1)	0	0
Anemia	0	0	1(2.0)	1 (2.0)
Cholelithiasis	2 (5.0)	0	0	0
Acute cholecystitis	2 (5.0)	0	0	0
Renal cyst hemorrhage	1 (2.5)	1 (2.6)	0	0
Pulmonary embolism	0	0	1 (2.0)	0
Myocardial infarction	0	0	0	1 (2.0)
Acute pyelonephritis	0	0	0	1 (2.0)
Ureteral obstruction due to lithiasis	0	0	0	1 (2.0)
Sepsis due to Klebsiella Pneumoniae	0	0	1(2.0)	0
Varicella	0	0	1(2.0)	0
Umbilical hernia	0	0	1(2.0)	0
Acute Pancreatitis	0	0	1(2.0)	0
Biliary vomiting	0	0	1(2.0)	0
Abdominal pain	0	0	0	1 (2.0)
Fever	0	0	1(2.0)	0
Pancreatic enzyme elevation	0	0	0	1 (2.0)
Hyperammonemia	0	0	1 (2.0)	0
Acute retinal detachment	0	0	1(2.0)	0
Genitourinary Prolapse	0	0	1(2.0)	0
Cystocele	0	0	1(2.0)	0
Menometrorrhagia	0	0	1(2.0)	0
Spinal column injury	0	1 (2.6)	0	0
Gastroenteritis	0	1 (2.6)	0	0
Hepatitis C	0	1 (2.6)	0	0
Hemorrhagic hepatic cyst	1 (2.5)	0	0	0
Nephrolithiasis	0	1 (2.6)	0	0
Intracranial aneurysm	1 (2.5)	0	0	0
Hypertensive crisis	0	1 (2.6)	0	0
Acute worsening of acute renal dysfunction	0	1 (2.6)	0	0

Data are n (%). LAR=long-acting release.

Preventing Progression to ESKD in Patients with Late Stage ADPKD: The ALADIN II trial

ALADIN II (Clinical trial gov: NCT01377246) was a prospective, randomized, single-center, placebo controlled clinical trial designed to assess the effect of Octreotide LAR on kidney volume and function over 3-year follow up in 100 ADPKD patients with a CKD stage 3b to 4 randomized to Octreotide LAR (n=51) or placebo (n=49). Patients with GFR < 15 ml/min/1.73 m^2 were excluded. We found that 3-year treatment with Octreotide LAR slowed kidney volume growth at 1 and at 3 years of follow up. Moreover, Octreotide LAR, as compared to placebo, slowed the progression to the combined endpoint of doubling of serum creatinine or ESKD (Figure 6, Top Panel). The effect was significant even after adjusting for age, sex, baseline serum creatinine (First pre-defined adjustment) and, in addition, total kidney volume (Second pre-defined adjustment). Notably, however, large part of the serum creatinine doubling events and all ESKD events were segregated in ALADIN II patients with CKD stage 4. An observational analysis showed that the protective effect of Octreotide LAR, not

only against progression to the combined end point (Figure 6, Middle Panel) but even against the progression to ESKD considered as a single endpoint (Figure 6, Bottom Panel) could be seen even in this subgroup considered separately. Again, the effect was significant even after adjusting for age, sex, baseline serum creatinine (First adjustment) and, in addition, for total kidney volume (Second adjustment). Finally, Octreotide LAR prevented the urinary protein increase observed in controls randomized to placebo.

Thus, our study provided the novel information that a somatostatin analogue may slow the progression to a hard clinical endpoint such as ESKD in patients affected by ADPKD. Only one-sixth of patients on Octreotide LAR progressed to the combined endpoint of ESKD or doubling of serum creatinine compared to twenty percent of those on placebo. Notably, only 4 patients needed to be treated to prevent 1 composite endpoint, and 10 to prevent 1 ESKD event considered as a single endpoint, during the 3-year follow-up. These findings may have implications for healthcare providers since postponing or even preventing ESKD, in addition to preserving patient quality (and expectancy) of life and physical function, also reduces the direct and indirect costs for chronic renal replacement therapy. All ESKD events were observed in patients with CKD stage 4, and the protective effect of Octreotide LAR against progression to the combined endpoint, or to ESKD considered as a single endpoint, was fully driven by treatment effect in this subgroup. In these patients, the reduction in event rates was associated with an acute GFR reduction at 6 months that conceivably reflected amelioration of compensatory glomerular hyperfiltration,[16,34,38–40] a tendency (admittedly non-significant) toward slower chronic GFR decline, and a protective effect against the increase in proteinuria observed on placebo. Thus, in ALADIN II patients with CKD stage 4, Octreotide LAR reduced the incidence of ESKD with only marginal effects on chronic GFR decline, an effect that conceivably could be explained by the extremely high number of ESKD events, which increased the power of event-based analyses compared to the power of slope-based analyses. Altogether, these data converge to indicate that even in later pre-terminal stages of ADPKD, when kidney architecture is largely disrupted, Octreotide LAR may still exert a specific and clinically relevant protective effect against progression of the disease.

Another finding that merits further investigation is that as already briefly mentioned for our pilot study and for the ALADIN trial - nephroprotection appeared to be partially explained by mechanisms—additional to those related to slowed kidney volume growth—similar to those of renin angiotensin system inhibitors, such as amelioration of hyperfiltration[34] and reduction of proteinuria, effects that in this specific context could be mediated by inhibited growth hormone secretion and action[41] and, notably, are not associated with hyperkalemia. As observed in other proteinuric chronic nephropathies,[45] these effects may protect residual functioning units from accelerated dysfunction and sclerosis. Thus, based on the above considerations, it is conceivable that proteinuria might be an additional risk factor for disease progression and a specific treatment target for Octreotide LAR in patients with ADPKD and CKD stage 4.[46]

Even in patients with severely impaired kidney function, Octreotide LAR was well tolerated, and no patient required treatment interruption or even transient dose down-titration during the study. The overall incidence of serious and non-serious adverse events was similar between groups (Table 3). However, the most interesting safety finding was that, despite the more advanced stage of disease in ALADIN II compared to the ALADIN trial patients, the safety profile of Octreotide LAR did not differ between the two trials. Morning fasting blood glucose was significantly higher in the Octreotide LAR than placebo group, but serum HbA1c values were similar between groups throughout the whole study period. Thus, it is conceivable that treatment impaired fasting blood glucose without appreciably affecting average blood glucose levels throughout the day. Consistently, no case of new-onset diabetes was observed in the Octreotide LAR group. As expected, diarrhea was more frequent in the Octreotide LAR group. However, in the affected 15 patients, it recovered spontaneously within 1 month from randomization. Biliary sand or stones were detected by routine ultrasound evaluation in 8 otherwise asymptomatic patients on Octreotide LAR, versus none on placebo, and dissolved in all cases with ursodeoxycholic acid supplementation. Adverse events that were most likely related to the disease, including renal cyst rupture or infection (which was serious in 4 cases), were more frequent in the placebo arm.

Overall, our present data confirm the good safety profile of Octreotide LAR reported in the ALADIN trial,[35] in a pilot safety study,[16] and in a small pilot trial.[47] However, these findings must be taken with caution since they were obtained by relatively small studies that, combined with the ALADIN II trial, included a total of only 131 patients with ADPKD who were exposed to Octreotide LAR for a relative short period, ranging from a minimum of 6 to a maximum of 36 months.

On the other hand, Octreotide LAR has been used for years in thousands of patients for the treatment of acromegaly[48] and neuroendocrine tumors,[49] and no major worrisome signal has emerged so far. Independent of the above considerations, however, data from larger series of ADPKD patients with longer exposure to treatment are needed to better establish the risk/benefit profile of Octreotide LAR in the specific context of ADPKD.

Octreotide LAR is a relatively expensive medication. The identification of a subgroup - accounting for approximately 10% to 15% of patients with ADPKD[50] - who are at high risk of ESKD and at the same time may benefit the most from treatment may help increase the cost-effectiveness of Octreotide LAR for the prevention of ESKD (and related treatment costs) in this population. Our data may pave the way to large-scale randomized trials with progression to ESKD as the primary outcome, to definitively demonstrate the nephroprotective effect of Octreotide LAR even in patients with less advanced (CKD stage 3) disease. This trial could also secondarily test the treatment effect on concomitant polycystic liver disease, cardiac function and morphology, and fatal and nonfatal major cardiovascular events.

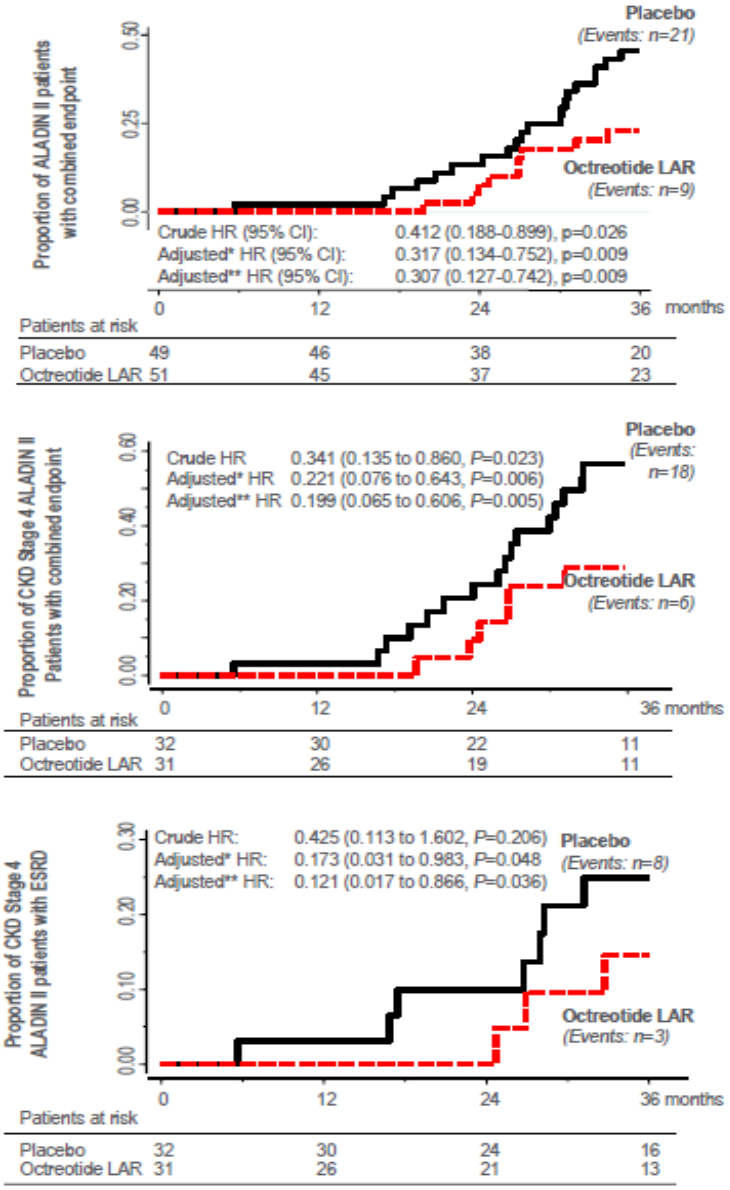

Figure 6: Kaplan-Meier curves describing the probability of ALADIN II patients with CKD stage 3b-4 to progress to the combined endpoint of doubling of serum creatinine or ESKD according to treatment with Octreotide LAR or placebo (Top Panel). Kaplan-Meier curves describing the probability of ALADIN II patients with CKD stage 4 considered separately to progress to the combined endpoint of doubling of serum creatinine or ESKD according to treatment with Octreotide LAR or placebo (Middle Panel). Kaplan-Meier curves describing the probability of ALADIN II patients with CKD stage 4 considered separately to progress to the single endpoint of ESKD according to treatment with Octreotide LAR or placebo (Bottom Panel Panel). *Adjusted by age, sex, and baseline serum creatinine, ** Adjusted by age, sex, baseline serum creatinine and total kidney volume

What not to Learn from a Randomized, Controlled Clinical Trial. Not all Somatostatin Analogues Were Created Equal

Results of the ALADIN II trial remarkably differ from those of the DIPAK 1 study,[51] an open-label randomized clinical trial with blinded endpoint assessment that tested the renal effects of 2.5-year treatment with Lanreotide, another long-lasting somatostatin analogue, in 309 patients with ADPKD who had an eGFR of 30 to 60 ml/min/1.73 m^2.

Unlike ALADIN II, DIPAK 1[51] failed to detect any treatment effect on severe worsening of kidney function - a surrogate for ESKD defined as a 30% decrease of eGFR compared to baseline - or start of dialysis. This finding is consistent with evidence that, in ALADIN II all ESKD events were observed in patients with CKD stage 4, and the protective effect of Octreotide LAR against progression to ESKD considered as a single endpoint or in combination with doubling of serum creatinine from baseline was fully driven by the treatment effect in this subgroup. Exclusion of patients with CKD stage 4 may explain why only 5 (3 on Lanreotide) of the 309 randomized patients (1.6%) progressed to ESKD during the DIPAK 1 study, compared to 11 of 63 patients with CKD stage 4 (17.5%) progressing to ESKD during the ALADIN II trial. Thus, unlike ALADIN II, DIPAK 1 was underpowered to detect a treatment effect on ESKD because of a markedly lower incidence of events in the study population. Notably, previous studies with Tolvaptan, that were aimed to detect treatment effect in ADPKD patients on the basis of changes in estimated GFR,[36] included much more than 1 thousand patients to find an average 1 ml/min/1.73 m^2 reduction in the rate of yearly eGFR decline with Tolvaptan as compared to placebo: a reduction that was statistically significant thanks to the very large sample size, but that at the same time was admittedly of uncertain clinical relevance. Unfortunately, in DIPAK1 the GFR was not directly measured by precise and accurate techniques.[30] The sample size however, was not adequately increased to obviate to this limitation that unavoidably increased random data fluctuations because of the large imprecision and inaccuracy of serum-creatinine-based GFR estimations;[52] a limitation that has been found to specifically apply also to patients with ADPKD.[53,54] Thus, DIPAK1 was underpowered (only 309 participants included as compared to the 1,455 of the Tolvaptan trial) for any considered outcome variable: 1. As for the detection of renal events, including the one pre-defined by the Authors, because the trial excluded *per protocol* specifically those patients who were at highest risk of events because of more severe renal insufficiency to start with. 2. As for the detection of a treatment effect on GFR decline because the GFR was not directly measured, but was just indirectly estimated. This approach would have required at least a five-fold larger sample size.[52]

An additional and plausible, but fully speculative, explanation for the differing results of these two studies could be that Lanreotide could be just less effective than Octreotide LAR in preventing ADPKD progression to ESKD. Indeed, different somatostatin analogues have different affinities for different sst1 to sst5 receptors expressed on kidney tubular cells, and in particular with sst2 which appears to be the receptor most directly involved in mediating the effects of somatostatin and its analogues on ADPKD cells.[55] Although Octreotide LAR and Lanreotide appear to have a similar affinity for sst2 receptor, it cannot be excluded that there might be other drug-specific differences between the two medications that could account for the lower (if any) nephroprotective effect of Lanreotide in ADPKD.[51] The hypothesis of different drug-specific effects is corroborated by the fact that in both ALADIN and ALADIN II trials we did not observe any episodes of hepatic cyst infection in participants given Octreotide LAR. This is at variance with the increased risk for hepatic cyst infection reported during treatment with Lanreotide in the DIPAK 1 study, especially in those with a previous history of hepatic cyst infection.[56] Moreover, severe hyperglycemia has been reported following transition from Octreotide to Lanreotide.[57]

Benefits of Octreotide LAR beyond Nephroprotection: OCTREOTIDE LAR AND THE LIVER - Polycystic liver disease (PLD) is a rare disorder arbitrarily defined by presence of more than 20 liver cysts.[58] It may occur as a genetically distinct entity,[59] but it may also be observed in up to 94% of patients with adult polycystic kidney disease (ADPKD).[60] Symptoms of PLD, including early satiety, gastro esophageal reflux, pain, and dyspnea, are caused by massive cyst and liver enlargement and may affect health-related patient quality of life, even severely.[61] Major functional complications include hepatic venous outflow obstruction, compression of the inferior vena cava, portal vein compression, or bile duct compression resulting in obstructive jaundice.[62] Cysts may also bleed or become infected, and cyst torsions or ruptures are rare but severe events.

For decades, treatment options relied on cyst aspiration and sclerotherapy or fenestration and even partial liver resection, which are invasive interventions that fail to affect cyst growth and disease progression.[23] Liver transplantation is the only rescue option for the most severe cases. Medical treatment of PLD has been limited to the use of analgesics for relief of pain and antimicrobial agents to treat infected cysts or biliary tract.[23]

Several years ago, we observed by serial comparative computed tomography scan analyses that renal and even liver volumes did not change appreciably during 2 years of follow-up in an ADPKD patient with PLD who was on continued treatment with long-acting release Octreotide LAR for a concomitant pituitary adenoma.[16] Combined

with our extensive experience in ADPKD and with evidence that in addition to renal tubular cells, also biliary tract colangiocytes express somatostatin receptors, in particular subtype 2, this observation further suggested that receptor activation by Octreotide therapy might also help prevent or limit biliary tract cells uncontrolled proliferation in patients with ADPKD and/or PLD. Indeed, as in renal tubular cells, proliferation and secretion of cholangiocytes are modulated by adenosine 3′, 5′-cyclic monophosphate (cAMP),[63] and fluid secretion via secondary transport of chloride can be curtailed by somatostatin, as it is in the rectal gland of the shark.[14] Consistently, a pilot crossover study showed that 6-month treatment with Octreotide LAR in addition to slow renal volume growth in patients with ADPKD,[16] even reduced liver volumes in those 12 patients who had concomitant PLD.[64] Subsequent experimental studies found that cAMP levels are increased not only in kidneys but also in livers of rats with polycystic disease, and Octreotide LAR may reduce both kidney and liver weights and mitotic indexes by reducing cAMP levels through interaction with specific tubular and biliary cells receptors.[65] Evidence that in our pilot study[16] changes in kidney and liver cysts were strongly and positively correlated during the treatment period with Octreotide LAR, whereas no relationship was seen between the two parameters during the placebo treatment period (Figure 7, Lower Panel), further corroborated the hypothesis of a common cAMP-mediated protective mechanism of Octreotide LAR in kidney as well as in liver cysts.[64] Notably, treatment effect on kidney and liver cysts was quantitatively very similar (Figure 7, Upper panel), as observed in the images of renal and liver CT scans taken from a representative patient on chronic Octreotide LAR therapy to treat ADPKD (Figure 8). The difference was that kidney cyst growth was faster and treatment effect resulted in a slowing or at best stabilization of cyst volume growth. Conversely, liver cysts showed a slower trend to growth over time and treatment with Octreotide LAR resulted in a further slowing of this growth that in some cases could even result in a net reduction of liver cyst volumes during the treatment period (Figure 7, Upper panel), -something that is only exceptionally observed with kidney cysts.

Thus, to assess the risk/benefit profile of long-term somatostatin inhibition, we took advantage of a single-center cohort of 27 patients with ADPKD and concomitant PLD allocated to 3-year treatment with Octreotide LAR (n=14) or placebo (n=13) in the context of the ALADIN trial.[35] After treatment completion, study patients were maintained on active follow-up to evaluate residual treatment effect during a 2-year off-treatment period and then were re-assessed (recovery evaluations).[66] In this 3-year prospective, randomized, placebo-controlled trial followed by a 2-year recovery period, we found that Octreotide LAR therapy achieved a significant and clinically relevant protective effect against progressive liver volume growth and was safe and well-tolerated in ADPKD patients with relatively early liver involvement. During the placebo-controlled study period, liver volumes decreased in Octreotide-treated patients, but continued to increase in controls. The benefit was sustained over time, and at the end of the recovery period liver volumes were still significantly smaller in patients originally randomized to Octreotide LAR than in those on placebo (Figure 9). In controls, TLVs progressively increased throughout the whole 5-year observation period, whereas in Octreotide-treated patients, final liver volumes were still slightly reduced compared with baseline (evaluated 5 years before). Thus, 3 years of Octreotide LAR therapy delayed disease progression by approximately 5 years (Figure 9).

In actual facts, in all patients liver volumes decreased during 3-year Octreotide LAR therapy, which actually slowed liver growth by almost 400 mL as compared with placebo, an effect that also translated into a significant volume reduction compared with baseline of about 120 mL.

The residual 10% liver volume reduction (corresponding to approximately 300 mL) we observed at 5 years in Octreotide LAR–treated patients compared with controls provided the additional information that treatment effect can be sustained even after treatment withdrawal. Prolonged patient exposure might also explain why despite the small sample size, we were able to detect a significant treatment effect even in men, a finding that challenges the previous belief that the benefit of somatostatin analogues is restricted to women, in particular to younger women, possibly because of estrogen-induced changes in intracellular signaling pathways.[67] Of note, treatment-induced reduction in TLV was relatively independent of liver volumes at inclusion, whereas liver growth on placebo was remarkably faster in patients with larger volumes. Consistently, the net benefit of Octreotide LAR vs. placebo was larger in patients with more severe hepatomegaly than in those with smaller livers to start with. These findings can be taken to suggest that Octreotide LAR therapy may have a specific indication for both male and female ADPKD patients with liver volumes exceeding approximately 1500–1600 mL, whereas larger studies with longer follow-up are needed to assess whether early intervention may help prevent progression to more advanced and

symptomatic stages of the disease in those with smaller livers.

The finding that liver volume reduction at 3 years exceeded by approximately 2-fold the volume reduction we previously observed during only 6-month treatment in a quite similar type of patients[64] suggested that, as observed in polycystic kidneys, treatment effect may be biphasic over time, with a faster short-term benefit followed by a sustained but to some extent slower effect in the long-term. As for kidney disease, this biphasic effect may be explained by 2 distinct and possibly overlapping mechanisms: (1) an immediate functional inhibition of cyst fluid secretion that may induce prompt cyst shrinkage and liver volume reduction, but which may wane shortly after treatment withdrawal,[68] and (2) a slower but progressive, time-dependent structural effect, possibly related to inhibited cholangiocyte proliferation and development and proliferation of new cysts,[65] which may substantially affect long-term disease progression.

Considering that Tolvaptan has no effects on polycystic livers and studies failed to demonstrate any benefit for mammalian target of rapamycin inhibitors, somatostatin analogues, and in particular Octreotide LAR, stand as the sole therapeutic option available for patients with PLD.

Altogether, these data and previous findings from the ALADIN trial[35] converge to indicate that in ADPKD patients, Octreotide LAR has a significant and clinically relevant curtailing effect on the growth of both liver and kidney cysts that is sustained over time. Treatment was remarkably safe and well-tolerated. Consistent with evidence that only approximately 1% of patients with Octreotide-induced gallstones have symptoms per year of treatment,[69] only 1 acute cholecystitis episode was observed, from which the participant recovered with medical therapy. Non-serious adverse events including diarrhea, flatulence, and abdominal pain were mild in nature and spontaneously waned shortly after randomization as expected, because the functional responses of the gastrointestinal tract and exocrine pancreas to somatostatin analogues are rapidly followed by local adaptation.[28] Thus, because of its remarkably good safety and tolerability profile, even life-long,[70] this medication appears to be a viable option for chronic therapy of ADPKD patients with or without polycystic livers. Early treatment of patients with polycystic liver disease may help prevent progression to more severe and potentially irreversible stages of the disease that may require invasive interventions to palliate symptoms that severely impact patient quality of life. Whether alternate on/off treatment periods may help improve the cost/effectiveness of chronic somatostatin inhibition therapy is worth investigating.

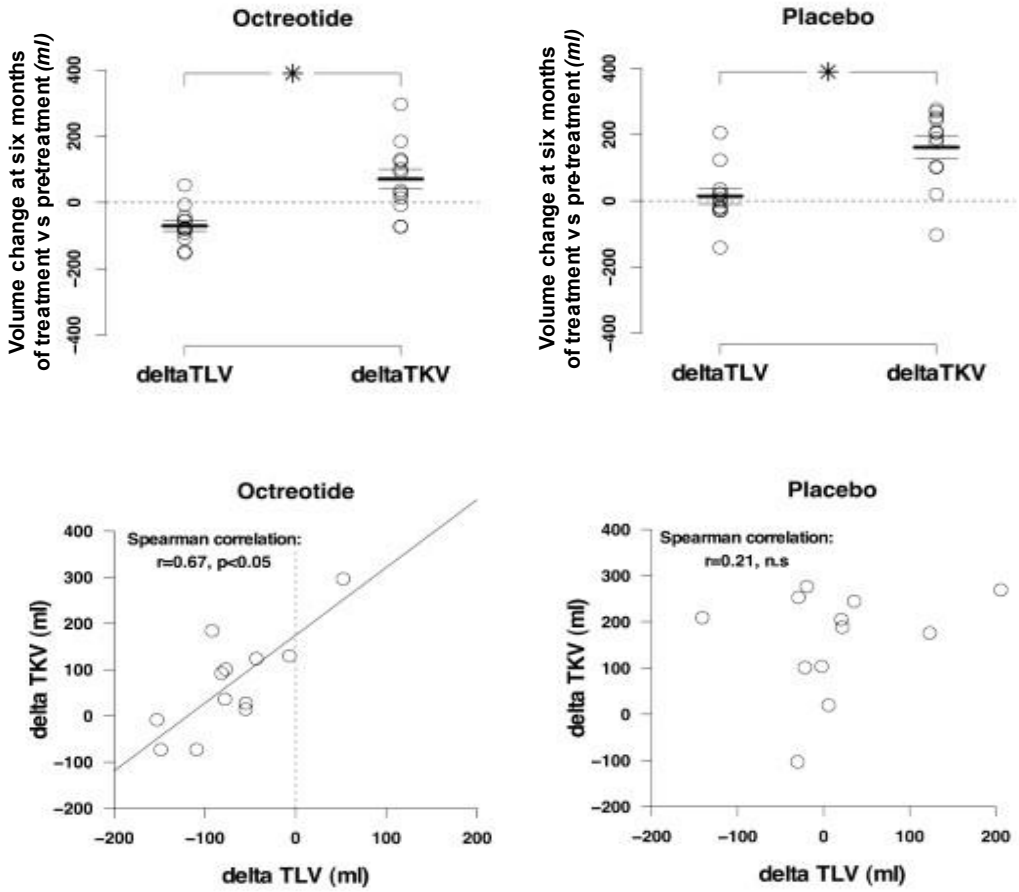

Figure 7: Effects of Octreotide LAR on total kidney and liver volumes in the same cohort of 12 patients with ADPKD and concomitant liver cysts (Upper Panels). Treatment effect on kidney and liver volumes appears to be similar, but the growth of kidney volume is faster and, at best, treatment effect translates into an almost stabilization of kidney volumes, whereas liver volume growth is slower. Thus, a similar treatment effect of Octreotide LAR translates not only into a slowing of liver volumes growth but even into a reduction in total liver volumes in some circumstances. The hypothesis of a causal relationship between Octreotide LAR therapy and inhibition of kidney and liver cyst growth was corroborated by finding that changes in total kidney volume and total liver volume during the Octreotide LAR treatment period in the same cohort of patients were significantly correlated, whereas no correlation was found between changes in both volumes during the same treatment period with placebo in the same cohort of patients (Lower Panels)

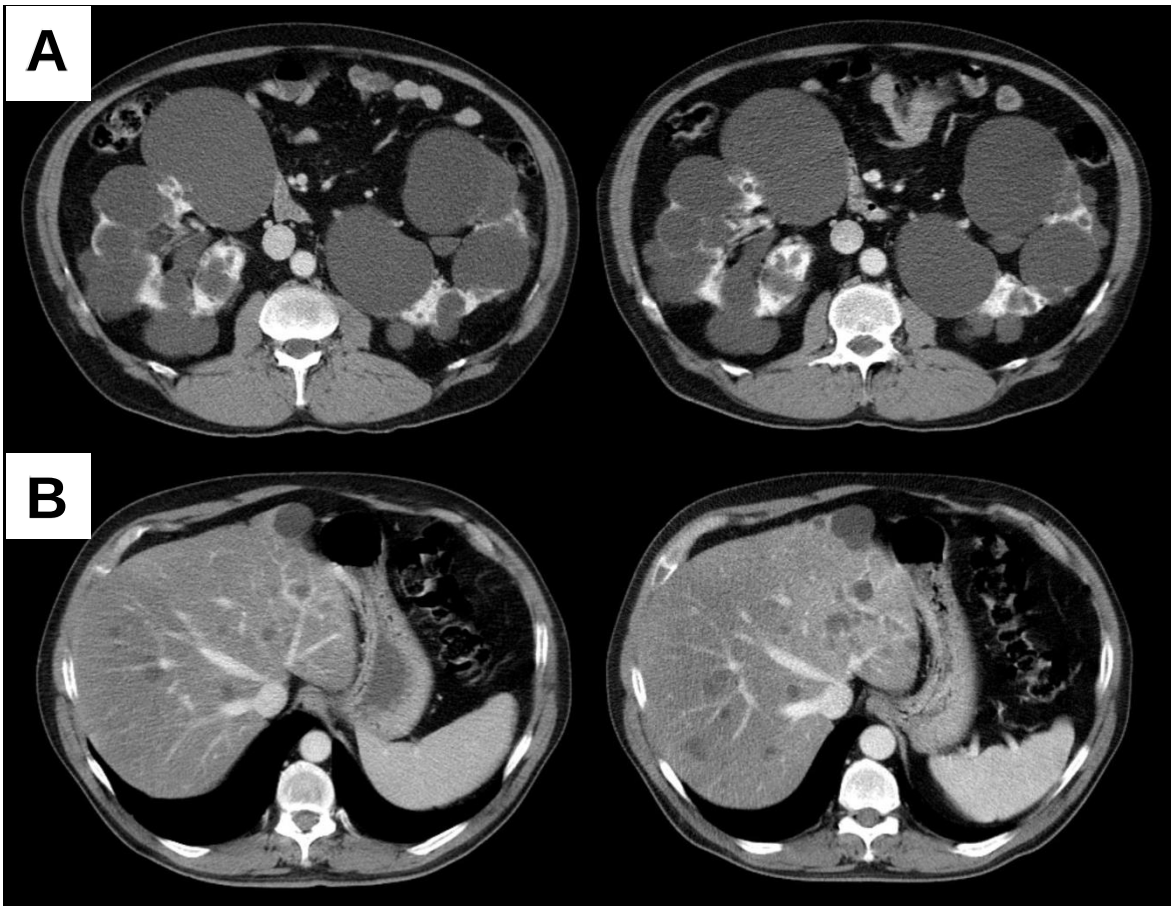

Figure 8: Kidney and liver and kidney and liver cyst diameters (Upper and Lower Panels, respectively) measured in abdominal CT scan evaluations taken one year a part (Baseline: Left Panels; 1-year: Right Panels) in a representative ADPKD patient on chronic Octreotide LAR therapy. Profiles of kidneys, liver and corresponding cysts at baseline and at 1-year of Octreotide LAR treatment are not appreciably different.

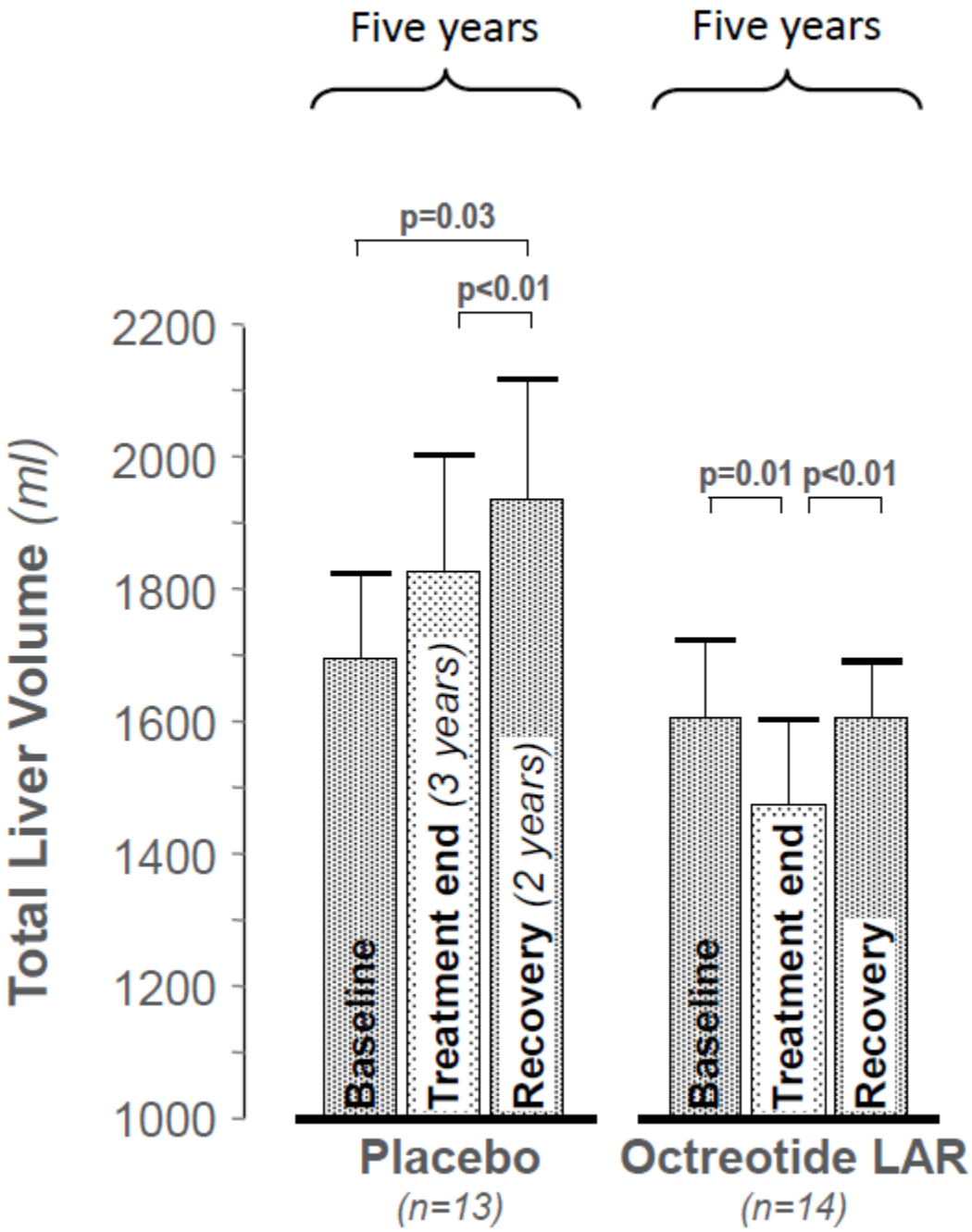

Figure 9: Total liver volumes at baseline, at completion of the 3-year treatment period with Octreotide LAR or placebo and after 2 years of recovery from any treatment in 27 ADPKD patients with concomitant polycystic liver disease randomly allocated to Placebo (Left Panel: n=13) or Octreotide LAR (Right Panel: n=14). During the whole 5-year observation, total liver volume significantly and progressively increased during the 3-year treatment period with placebo vs. baseline and at the end of the recovery period continued to significantly increase as compared to the end of the treatment period (Left Panel). During the same 5-year observation period, total liver volume significantly decreased during the 3-year treatment period with Octreotide LAR as compared to baseline and then significantly increased at the end of the recovery period as compared to the end of the treatment period. Thus, at the end of the whole 5-year observation period total liver volume was stabilized (Right Panel).

OCTREOTIDE LAR AND THE HEART – Both PC1 and PC2 proteins are expressed in cardiomyocytes and appear to elicit a direct effect on cardiac cell performance.[66,71–73] As for tubular cell and cholangiocytes, the genetically determined PC1 or PC2 dysfunction in ADPKD patients may result in decreased intracellular calcium inflow with increased cAMP production and activation of cAMP-mediated mechanisms which contribute to cyst cell growth in other organs.[74] Impaired ventricular

ejection fraction has been demonstrated in mice lacking PC1 in hearts.[72] PC2-deficient zebrafishes had heart with altered calcium signal and developed a systolic and diastolic dysfunction.[75] Thus, the alteration of polycystins in the heart could directly contribute to cardiac remodeling in patients with ADPKD even in the absence of renal failure or high blood pressure (BP). Somatostatin receptor subtypes are expressed on both myocytes and myocardial fibroblasts.[76] Conceivably, binding of these receptors by Octreotide LAR could limit or prevent early myocardial dysfunction in patients with ADPKD through mechanisms similar to those that modulate cyst generation and growth in kidney and liver.

We tested this hypothesis by using speckle-tracking echocardiography allowing analysis of myocardial tissue deformation by quantifying tissue strain and strain rate. Left ventricular (LV) longitudinal strain is a sensitive marker of very early myocardial dysfunction.[77–79] The assessment of LV rotational dynamics by speckle tracking echocardiography has been validated versus magnetic resonance imaging.[80–82] Impaired diastolic untwisting motion of the LV along its longitudinal axis can herald early LV diastolic dysfunction.[83]

Thus, we used speckle-tracking echocardiography to assess whether and to what extent LV function is impaired in patients with ADPKD and can be improved by Octreotide LAR in a two phase cross-sectional matched-cohort study, followed by a longitudinal, randomized phase conducted within the ALADIN trial (Please see *Supplementary Figure* in the *Supplementary Material)*.

In the cross-sectional phase we found that LV function was significantly impaired in the 34 ADPKD patients as compared to the 34 age- and gender-matched healthy controls with normal kidney function and to the 34 age-, gender-, and serum creatinine- matched renal controls with comparable kidney dysfunction, whereas it did not differ appreciably between the two control groups. Although all participants had functional NYHA class 1 and normal LV ejection fraction, ADPKD patients showed subclinical systolic dysfunction with reduced LV global longitudinal strain and twist in association with LV diastolic dysfunction. In the 3-year longitudinal, randomized phase, however, both LV systolic and diastolic function improved significantly in the 16 ADPKD patients on Octreotide LAR as compared to the 18 controls on placebo (Figure 10). Thus, at study end no statistically significant difference in LV function could be observed between Octreotide LAR-treated ADPKD patients and healthy controls. Conversely, the large difference observed between placebo-treated ADPKD patients and both control groups at baseline was still evident at study end. Moreover, placebo treatment was associated to a slight but significant decrease in LV ejection fraction.

Altogether, these findings indicate that early LV dysfunction in ADPKD patients is mediated by disease-specific mechanisms that appear to be directly affected by Octreotide LAR. Whether the improvement in cardiac function was mediated by an inhibitory effect of Octreotide LAR on cAMP production in myocardial cells is an intriguing but plausible hypothesis. Indeed, this hypothesis was corroborated by finding that active treatment with Octreotide LAR ameliorated both systolic and diastolic LV function, independent of BP control. Somatostatin receptor subtypes sst1, sst2, sst4 and sst5 are uniformly expressed in human atrial and ventricular tissue.[76] In cultured human cardiac fibroblasts, somatostatin induces a rapid and significant mobilization of intracellular calcium also eliciting a positive inotropic effect in ventricular muscle.[76,84] Thus, it is conceivable that the effects of Octreotide LAR on LV dysfunction could be at least in part explained by inhibition of Ca^{2+}- mediated mechanisms, through different somatostatin receptor subtypes expressed in the human heart. Interestingly, the persistence of reduced longitudinal and rotational function in ADPKD patients treated with placebo was associated at 3-year follow up with a decline in LV ejection fraction. Hence, cardiovascular manifestations of disease are the major contributors to mortality in ADPKD.[85] Thus, LV function is impaired in ADPKD patients with normal or moderately reduced kidney function and is ameliorated by Octreotide LAR. Somatostatin analogues in addition to prevent hepatorenal cystogenesis,[16,35,86] and limit long-term GFR decline,[35] can also help improving or preventing LV dysfunction in this population.

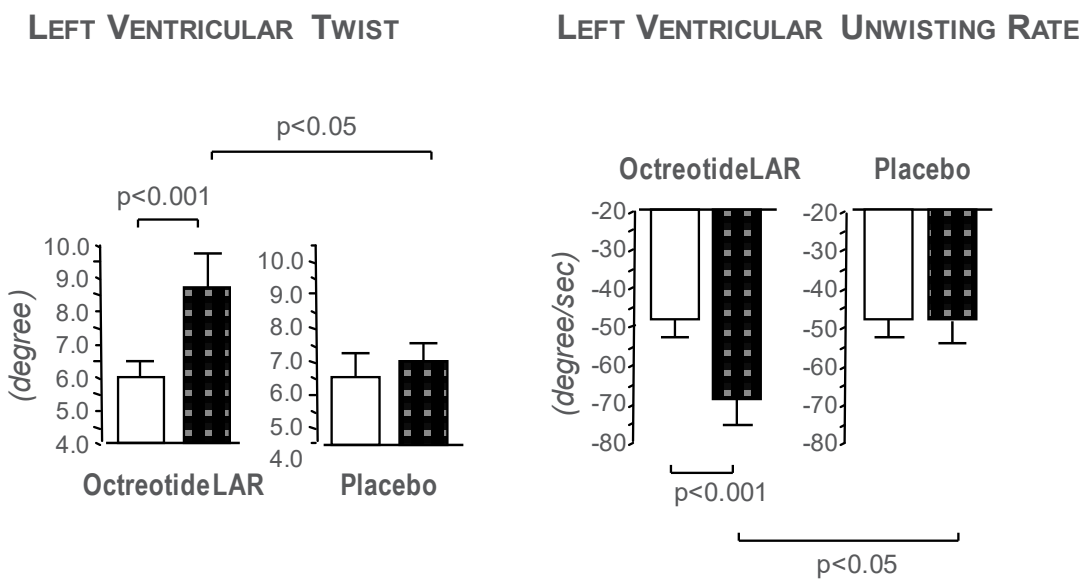

Figure 10: Changes in LV Twist (Left Panel) and LV untwisting rate (Right Panel) as assessed by speckle-tracking echocardiography during the ALADIN trial in patients randomized to Octreotide LAR or Placebo. At the end of 3-year treatment period with Octreotide LAR LV (Black Bars) Twist significantly increased (Left Panel) and LV Untwisting Rate significantly decreased (Right Panel) as compared to baseline (White Bars), whereas the two parameters did not change appreciably during the 3-year treatment period with Placebo.

Better Octreotide LAR or Tolvaptan? Or a Right Dose of Both? Again, from the Bench to the Perspective of a Prospective, Randomized Clinical Trial

In their seminal study, Hopp K and coworkers[24] have demonstrated in a slowly progressive model of PKD1 the value of treatment with Tolvaptan or Pasireotide alone and the additive effect of combined therapy, suggesting that using both means to lower cAMP levels would be beneficial in the human disease. Using the combination of both drugs may also allow lower single drug doses, achieving similar results but limiting adverse events. The benefit was seen in terms of percent reduction in kidney weight/body weight ratio, cystic and fibrotic volumes, and cAMP levels for the combined treatment. Interestingly, the effect of Pasireotide was generally greater than that of Tolvaptan. In addition, Pasireotide treatment showed a slight antidiuretic effect, which may benefit patients treated with both drugs because it could reduce aquaresis-related symptoms induced by Tolvaptan. Further, Pasireotide corrects the hepatic hypertrophy observed in the inbred *PKD1*$^{RC/RC}$ model, an abnormality that may be present but unrecognized in patients, masked by polycystic liver disease.

Thus, clear-cut basic evidence is available that vasopressin antagonists and somatostatin analogues, which indirectly reduce adenylcyclase 6 activity, markedly reduce renal tubular cell proliferation and cyst growth in experimental models of ADPKD, an effect that is associated with reduction in renal cAMP levels with both medications.[87,88] Preliminary experimental evidence is also available that in combination, the two treatments show an additive effect and may significantly reduce renal cystic and fibrotic volume as well as cAMP levels to wild type levels.[24] These findings highlight the likely benefit of combination therapy for patients with ADPKD.

Indeed, both the vasopressin V2 antagonist Tolvaptan and the somatostatin analogue Octreotide LAR effectively slow TKV and CKV

growth and GFR decline in patients with ADPKD.[35,36] Moreover, with both medications changes in TKV and CKV show a biphasic trend, with a larger acute (and reversible) reduction that can be observed within weeks or months[16,37,89] followed by a chronic effect that progressively manifests over years of follow up,[35,36] even in patients with stage 4 CKD.[90] The effect on TKV and CKV is larger during initial treatment possibly because fluid secretion into cysts acutely decreases shortly after the initiation of treatment[16,37,89] 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[16,35,37,89] of glomeruli surviving cyst-induced structural damage[34] followed by a slower decline long-term that is most likely mediated by inhibited renal 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 analogues such as Lanreotide that showed no renoprotective effects in ADPKD patients with Stage 3 CKD.[51] 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 (RPF).[89] The short-term effects of both medications appear to be larger when the GFR is normal or even higher than normal.[91] Evidence that in this context Tolvaptan and Octreotide LAR both acutely reduce the GFR and that larger short-term reduction correlated with a slower long-term GFR decline,[35] converge to indicate that at this stage of the disease kidney function is characterized by compensatory glomerular hyperfiltration and that this hemodynamic change is reversible.[34]

On the basis of experimental data,[24] it is conceivable that Tolvaptan and Octreotide LAR should have an additive effect also in human disease. Thus, initial GFR, TKV and CKV reduction should be larger with Tolvaptan and Octreotide LAR combination therapy than with Tolvaptan or Octreotide LAR monotherapy. To address this working hypothesis we designed a pilot trial (TOOL Trial, Clinical trial gov: NCT03541447) to compare the short-term effects of Tolvaptan and placebo combination therapy vs. Tolvaptan and Octreotide LAR add-on therapy on directly measured GFR,[30] TKV, CKV, and kidney functional parameters as assessed by magnetic resonance imaging (MRI) in a homogeneous cohort of patients with ADPKD. The results of this short-term study should hopefully pave the way for a prospective randomized long-term clinical trial to compare the long-term nephroprotective effect of combination therapy with that of Tolvaptan and, ideally, Octreotide LAR monotherapy. This trial will also offer the unique occasion to compare the effects of the two study treatments on liver cyst growth and cardiac dysfunction typical of ADPKD.

Conclusions and Perspectives

Confirming that Octreotide LAR add-on therapy could safely enhance the beneficial effect of Tolvaptan on compensatory glomerular hyperfiltration and contribute to reduce total kidney and cystic volumes in a homogeneous cohort of ADPKD patients with normal kidney function could pave the way to novel trials in patients with more advanced stages of ADPKD, who could benefit the most from a more effective nephroprotective intervention that could substantially slow renal disease progression and postpone/prevent the risk of progression to ESKD. Confirming that Octreotide LAR may also limit the acquaretic effects of Tolvaptan would also have major implications because massive polyuria and nocturia are major limitations to patient compliance to chronic Tolvaptan therapy. Availability of orally active Octreotide (Mycapssa)[92] would also facilitate the finalization of long-term clinical trials and the treatment of ADPKD patients in everyday clinical practice with fixed oral combinations of Octreotide LAR and Tolvaptan.

AUTHOR CONTRIBUTIONS

PR had the original idea, wrote the initial draft and the final version of the manuscript. Both PR and GR contributed to ideation, conduction and analyses of all the clinical studies mentioned in the manuscript. As for all these studies, AP performed the statistical analyses and contributed to data interpretation, AC revised the radiological material and analyzed kidney and liver scans, NP and MT contributed to the conduction and finalization of the clinical studies, APi and LS ideated and conducted the sub-studies evaluating the liver and cardiac effects of Octreotide LAR in a subgroup of ALADIN ADPKD patients. All Authors were involved in interpretation of data, critically revised the first draft and approved the final version of the manuscript. No medical writer was involved.

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DISCLOSURES

The authors have no conflict of interest to declare.

DATA SHARING INFORMATION

Sharing of individual participant data with third parties was not specifically included in the informed consent of the studies considered in this descriptive review and unrestricted diffusion of such data may pose a potential threat of revealing participants' identity, 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 three months and up to five years from study conclusion and/or article publication. Researchers shall submit a methodologically sound proposal. To gain access to data requestors will need to sign a data access agreement and obtain approval of the local ethics committee.

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