Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease

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Background. The fluid filling renal cysts in human polycystic kidneys is secreted chiefly by the tubular epithelium lining the cysts via secondary chloride transport. Inhibiting this process by somatostatin therapy should induce shrinking of renal cysts.

Methods. In this randomized, cross-over, placebo-controlled trial we compared the risk/benefit profile of 6-month treatment with long-acting somatostatin (octreotide-LAR, 40 mg intramuscularly every 28 days) or placebo in autosomal-dominant polycystic kidney disease (ADPKD) patients with mild-to-moderate renal insufficiency and no evidence of other kidney disease. Volumes of kidney structures were evaluated by a two-slice computed tomography (CT) scanner; while glomerular filtration rate (GFR) was estimated by iohexol plasma clearance.

Results. One patient on somatostatin and one on placebo were prematurely withdrawn because of nonsymptomatic, reversible colelithiasis and asthenia, respectively. In the remaining 12 patients somatostatin was well tolerated. Kidney volume increased by 71 ± 107 mL (P < 0.05) on somatostatin and by 162 ± 114 mL (P < 0.01) on placebo. The percent increase was significantly lower on somatostatin (2.2 ± 3.7% vs. 5.9 ± 5.4%) (P < 0.05). Cystic volume tended to increase less on somatostatin than on placebo (3.0 ± 6.5% vs. 5.6 ± 5.8%). The “parenchymal” volume nonsignificantly increased by 2.5 ± 8.4% on placebo and slightly decreased by 4.4 ± 8.9% on somatostatin. The GFR did not change significantly during both treatment periods.

Conclusion. In ADPKD patients, 6-month somatostatin therapy is safe and may slow renal volume expansion. This may reflect an inhibited growth in particular of smallest cysts beyond the detection threshold of CT scan evaluation. Whether this effect may prove renoprotective in the long term should be tested in additional trials of longer duration.

1These authors contributed equally to this work.

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secondary active chloride transport [9], is also responsible for secretion of fluid into the lumen by proximal renal tubules in teleost and elasmobranch fishes [10, 11] and in the rectal (salt-excreting) gland of elasmobranchs [12]. In the shark, rectal gland chloride secretion is markedly inhibited by somatostatin in a way suggesting inhibition of adenylate cyclase and of post-cyclic adenosine monophosphate (cAMP) events as well as an inhibition of secretion stimulated by agents that do not generate cAMP [13, 14]. Evidence that specific receptors for somatostatin are present in human kidneys [15] suggests the possibility that somatostatin treatment of patients with ADPKD might inhibit fluid formation and eventually induce shrinking of renal cysts.

Somatostatin is a cyclic 14 amino-acid peptide secreted by pancreatic islets (D cells), gastrointestinal tract, nervous system, and thyroid gland [16]. There are two native biologically active forms of somatostatin, and a number of synthetic analogues have been described [17]. 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 present in kidney tissue, and shows a high affinity for the somatostatin analogue octreotide [15]. Effector systems of sst2 receptors are inhibitors of adenylate cyclase and stimulators of phosphatase and phospholipase C [16]. Recently somatostatin analogues have become available and have been used with negligible side effects for long-term treatment (up to 8 to 12 months) of multiple endocrine tumors [18].

We suspected a potentially beneficial effect of somatostatin in patients with ADPKD from observing a female patient on continued treatment with the somatostatin analogue octreotide for about 2 years to prevent 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 treatment was started and 2 years later failed to detect any appreciable change in cyst areas (Fig. 1). This finding, combined with a stable serum creatinine concentration, suggested possible inhibition of the growth of renal cysts that might have prevented further damage to the residual functioning kidney parenchyma. We therefore designed a pilot study to assess the safety-profile and the structural and functional effects of a long-acting somatostatin in patients with ADPKD and varying degrees of renal insufficiency. The results of this clinical study form the basis of the present report.

METHODS

This randomized, longitudinal, cross-over study compared the safety and efficacy of treatment for 6 months with long-acting somatostatin or placebo in adult patients with ADPKD. The safety and tolerability of somatostatin treatment was assessed by comparing the incidence of serious and nonserious 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, determined by spiral CT scan evaluations, and GFR, as determined by iohexol plasma clearance [19], recorded at baseline and at the end of each treatment period. The morpho-functional relations between concomitant changes in kidney volumes and GFR during treatment period and during placebo were also evaluated. The study protocol was approved by the Ethical Committees of the Clinical Research Center for Rare Diseases of the Mario Negri Institute and of the Azienda Ospedaliera Ospedali Riuniti di Bergamo. Before inclusion, eligible
patients provided their written informed consent according to the Declaration of Helsinki guidelines.

**Patient selection**

Patients aged 18 years or older, with a clinical and echographic diagnosis of ADPKD and a serum creatinine concentration <3.0 mg/dL, but >1.2 mg/dL (males) or >1.0 mg/dL (females) were selected for study participation. Patients with concomitant systemic, renal parenchymal or urinary tract disease, diabetes, overt proteinuria (urinary protein excretion rate >1 g/24 hours), or abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease, urinary tract lithiasis, infection or obstruction, biliary tract lithiasis or obstruction, more than two hemorrhagic or complicated cysts, cancer and major systemic diseases that could prevent completion of the planned follow-up or interfere with data collection or interpretation, psychiatric disorders, and any condition that could prevent full comprehension of the purposes and risks of the study were not considered eligible for study participation. Pregnant or lactating women or fertile women without effective contraception were also excluded from the study.

**Study design**

At a screening visit, potentially eligible patients had an ultrasound evaluation of the kidneys and liver. Those with no evidence of urinary tract or gallbladder lithiasis and satisfying all the other inclusion/exclusion criteria entered the study. After 5 minutes rest in sitting position, they had three blood pressure measurements (Korotkoff phase I and V) taken by a standard sphygmomanometer 2 minutes apart at the dominant arm, and the mean of the three readings was recorded for statistical analyses. Blood and urine samples were taken in the morning with the patient fasting from the evening before, for routine laboratory evaluations, including routine hematochemistry, renal and liver function tests, and coagulation tests. The GFR was measured by the iohexol plasma clearance technique, as described in details previously [19]. 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 below.

After baseline evaluations, patients were randomly allocated to start a 6-month treatment period with the long-acting somatostatin octreotide-LAR (Sandostatin-LAR® Depot; Novartis Pharma AG, Basel, Switzerland) or with placebo (40 mg intramuscularly for 28 days, given as two intragluteal 20 mg injections). Every 2 months blood pressure and routine laboratory tests, including blood glucose, serum creatinine, creatinine clearance, complete blood cell count, and 24-hour urinary protein excretion rate, were evaluated and a kidney and liver ultrasound evaluation was repeated. At 6 months, all the measurements performed at baseline evaluation (including CT and GFR evaluations) were repeated. Then, each patient crossed over to the other treatment arm. The same measurements performed during the first treatment period were repeated every 2 months and at completion of the second treatment period, all baseline evaluations were repeated before patients were discharged from the study.

No specific change in diet and pharmacologic treatment was introduced throughout the study period, unless deemed clinically appropriate to control blood pressure or limit the signs of renal or liver dysfunction. In particular only adjustments in the doses of the ongoing antihypertensive treatments were recommended in order to maintain the same level of blood pressure control (target systolic/diastolic blood pressure <130/80 mm Hg) throughout the whole study period. Concomitant changes in blood glucose levels and need for antidiabetic therapy throughout the study period were carefully monitored since they could be taken as indirect evidence of an unfavorable effect of somatostatin therapy on insulin sensitivity and glucose metabolism.

**Spiral CT scanning and volumetric analyses**

Volumes of kidney structures were evaluated by a twoslice CT scanner (CT-Twin) (Elscint, Haifa, Israel). A single breath-hold CT scan was used to eliminate artifacts due to respiratory motion. CT acquisitions were started 90 seconds after start of an intravenous injection of 170 mL of nonionic contrast agent (Iopamiro) (Bracco, Milano, Italy) at a rate of 2.5 mL/second. Main scanning parameters were maintained constant for all acquisitions (voltage 120 kV, current 230 mA, field-of-view 43 cm, matrix 512 × 512, collimation 5 mm, pitch 1, increment 3 mm, and overlap >50%). Digital CT images were transferred to a PC workstation in Dicom format and used for digital morphometry, using in-house developed software (C++ and Insight Toolkit, ITK) [www.itk.org] [20]. Briefly, kidneys were initially outlined by a trained radiologist (G.F.) with manual operation on digital images. The operator was not required to identify precisely the kidney boundary where a fat region surrounded the organ, but to place the outline at the organ interface when other tissues, such as the liver, were in contact with the kidney. The total volume of the right and left kidney, of the parenchyma and of the cysts was evaluated by automatic segmentation of kidney images. To obtain this result images were initially enhanced by anisotropic diffusion filtering [21] whose implementation is available in the ITK library. After smoothing image segmentation was performed by a histogram-based statistical approach known as Otsu’s thresholding [22]. Briefly, in this method the image intensity histogram is
partitioned in a previously assumed number of classes \((N = 3)\) as to minimize the between-class variance. Intensity of image pixels of the kidney were then assigned automatically to one of these areas, respectively, the parenchyma, the cysts, and an intermediate area that we considered to be a transition from parenchyma to cyst area likely deriving from the partial volume effect. A representative example of this image segmentation is reported in Figure 2. The number of pixels of the parenchyma and cysts areas was used to calculate total volume of these structures in left and right kidney, taking into account pixel dimensions as contained in Dicom images and the distance between two slices. Thus, two volumes were identified, a cystic volume and parenchymal volume. The cystic volume included cysts of approximately 3 mm in diameter or larger, the parenchymal volume included apparently normal parenchyma as well as parenchyma with early changes consisting of initial tubular dilatation and small cysts below the detection threshold of the CT scans. To account for this approximation, this volume was identified by the term parenchymal volume inserted between inverted commas. The residual kidney tissue, accounting for about 20% of the total kidney volume, could not be unequivocally assigned to either cystic or parenchyma volume and was not considered in the analyses. A three-dimensional representation of these kidney volumes is reported in Figure 3. The results of image segmentation were verified by an expert radiologist. Finally, the accuracy of volume measurements was evaluated as previously described by King et al [5] using a phantom. This validation permitted to estimate a mean error between calculated and actual volumes of the phantom to be less than 0.7%.

Statistical analysis

This was an exploratory study aiming to have at least ten patients available for full-set analyses, a figure considered a priori to provide a reasonable sample size for a preliminary evaluation of the efficacy and safety profile of the study drug. Two factors—the availability of a sensitive and reproducible technique such as spiral CT allowing for precise volumetric evaluations, and the cross-sectional design preventing the confounding effect of between-patients variability—were expected to permit powerful analyses with a relatively small sample size. Data are given as mean ± standard deviation (SD) or median and range as specified.

RESULTS

Baseline characteristics

Fourteen patients entered the study. A positive family history for ADPKD was obtained for each subject. On the basis of the history, nine patients had the PKD1 form and one the PKD2 form (as suggested also by the linkage analysis). In the remaining four subjects the differential diagnosis between PKD1 and PKD2 was uncertain. One patient was withdrawn after 5 months of somatostatin therapy because of the detection at routine ultrasound
evaluation of two, nonsymptomatic, small gallstones that dissolved after 2 months’ treatment with ursodeoxy-
cholate acid. Another patient was withdrawn after 3 months of placebo treatment because of asthenia. Thus, 12 patients (nine males and three females) completed the study. Their main characteristics at study entry are summarized in Table 1. Two patients were normotensive. The remaining ten patients were on renin-angiotensin system (RAS) inhibition therapy, with ACE inhibitors (N = 9) or an angiotensin II receptor blocker (N = 1). In five patients the RAS inhibitor was a component of a multidrug regimen that included a beta blocker (N = 1), a beta blocker and a calcium channel blocker (N = 1), a diuretic and a calcium channel blocker (N = 2), or a diuretic and a beta blocker (N = 1). Nine patients had a serum creatinine equal to or greater than 1.3 mg/dL. In four patients urinary albumin was within normal limits; seven were microalbuminuric and one was macrolbuminuric.

Table 1. Demographic, clinical, and kidney structural data at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>44.5 (35-58)</td>
</tr>
<tr>
<td>Systolic blood pressure mm Hg</td>
<td>144.1 ± 11.6</td>
</tr>
<tr>
<td>Diastolic blood pressure mm Hg</td>
<td>94.2 ± 11.9</td>
</tr>
<tr>
<td>Serum creatinine mg/dL</td>
<td>1.9 (1.0-3.4)</td>
</tr>
<tr>
<td>Glomerular filtration rate mL/min/1.73 m²</td>
<td>57.1 (24.4-95.3)</td>
</tr>
<tr>
<td>Albuminuria µg/min</td>
<td>27 (9-437)</td>
</tr>
<tr>
<td>Resistive index, left</td>
<td>0.61 ± 0.07</td>
</tr>
<tr>
<td>Resistive index, right</td>
<td>0.63 ± 0.06</td>
</tr>
<tr>
<td>Kidney volume mL</td>
<td>2435 ± 966</td>
</tr>
<tr>
<td>Cyst volume mL</td>
<td>1631 ± 838</td>
</tr>
<tr>
<td>Parenchymal volume mL</td>
<td>242 ± 61</td>
</tr>
<tr>
<td>Residual volume mL</td>
<td>562 ± 277</td>
</tr>
</tbody>
</table>

Data are mean ± SD or median and (range).

Mean values of kidney volumes, as determined by CT investigation and digital image processing are reported in Table 1. Total (left + right) kidney volumes were quite heterogeneous within the study group, ranging from 1498 to 4294 mL. Five patients had a total kidney volume
larger than 2 L. Most of the kidney volume was occupied by radiologically detectable cysts averaging 65% (range 52% to 86%). Ten patients had a GFR below the normal range (80 to 120 mL/min/1.73 m²). There was a marginally significant correlation between GFR and parenchymal volume (r = 0.52, P = 0.08). No correlation was found between GFR and total or cyst volume. The resistive index of both kidneys was below 0.80 in all patients.

**Safety and tolerability**

Somatostatin treatment was well tolerated in all patients who completed the study. Watery diarrhea was reported in three patients and spontaneously recovered in all within the first month of treatment. As shown in Table 2, blood pressure was relatively well controlled without significant changes throughout both treatment periods. No change in antihypertensive therapy was introduced in any patient during placebo or during treatment period. The resistive index with somatostatin or placebo in each individual patient is shown in Figure 4. On average, the volume of both kidneys significantly increased by 71 ± 107 mL (P < 0.05) during somatostatin treatment and by 162 ± 114 mL (P < 0.01) during placebo (Table 3) (Fig. 5). Thus, on somatostatin 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 3) (Fig. 5). The increase in kidney volume during treatment with somatostatin 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 3) (Fig. 5).

As reported in Figure 5, on somatostatin treatment the percent change in total kidney volume was significantly lower than on placebo (2.2 ± 3.7% vs. 5.9 ± 5.4%, respectively) (P < 0.01). This difference was the result of a numerically lower growth of cyst volume on somatostatin 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 somatostatin, but actually increased by 2.5 ± 8.4%, on placebo (Fig. 5). There were no significant correlations between changes in total kidney, parenchymal or cyst volumes, and concomitant changes in GFR or serum creatinine, or resistive index throughout both treatment periods.

**Renal functional analysis**

As reported in Table 3, GFR did not change significantly on placebo or on somatostatin. Serum creatinine numerically increased both during placebo and treatment period, but these changes did not reach statistical significance. Albumin excretion rate did not change either during placebo or during treatment period. The resistive index throughout both treatment periods.
index did not change significantly throughout either treatment periods (Table 2).

**DISCUSSION**

The hypotheses driving the present study were (1) that the growth of renal cysts in polycystic kidneys over time represents a slight cumulative excess of secretion over reabsorption and (2) that the process of secretion (via secondary active transport of chloride) might be inhibited by somatostatin, as it is in the rectal gland of the shark [13, 14].

We found that in adult patients with ADPKD and different degrees of renal insufficiency, treatment for 6 months with the somatostatin analogue octreotide was safe and well tolerated. Moreover, octreotide, as compared to placebo, retarded the time-dependent increase in total kidney volume to a significant extent. The net
effect on kidney volume resulted from an action of the drug on cyst volume and on parenchyma volume. While the volume of radiologically detectable cysts was not appreciably reduced by somatostatin treatment, average “parenchymal” volume was reduced while on active treatment, but increased on placebo. The GFR was marginally correlated with “parenchymal volume,” but not with total or cyst volumes, and tended to decrease on octreotide.

Of note, despite the different procedures used for the evaluation of kidney volumes and function [spiral CT scanning and iohexol plasma clearance versus magnetic resonance imaging (MRI) and iothalamate renal clearance, respectively] the morphologic and functional data in our present series were very well comparable with those in the remarkably larger series of patients with similar clinical characteristics included in the Consortium for Radiologic Imaging Studies of Polycystic kidney disease (CRISP) [23].

Safety

Only one patient had to interrupt somatostatin therapy prematurely because of asymptomatic cholelithiasis that disappeared after a few months of treatment with ursodeoxycholate acid. Octreotide has occasionally been reported to favor the development of gallstones, that, however, promptly dissolved by ursodeoxycholic acid [24]. Three patients reported a watery diarrhea that spontaneously recovered during the first month of somatostatin therapy; this has also been occasionally reported as a side effect of octreotide treatment. No deleterious changes in laboratory parameters were observed during somatostatin therapy. In particular, in the study group as
a whole there were no significant changes in blood glucose and hemoglobin A1c (HbA1c) levels. In one patient on placebo, however, there was an increase in blood glucose above 125 mg/dL that did not require pharmacologic treatment. These reassuring findings are consistent with previous evidence that chronic treatment with somatostatin occasionally increased fasting blood glucose and HbA1c, or reduced glucose tolerance, but never caused new onset diabetes [25]. Finally, we observed a marginal and transient increase in alanine aminotransferase levels, without any other change in liver function parameters, in two patients on somatostatin and in one on placebo. These abnormalities recovered spontaneously and may have been related to concomitant cystic disease of the liver.

Efficacy

The heterogeneous effects on cystic and “parenchymal” volumes most likely reflected different effects of somatostatin therapy in modulating the development and growth of cysts at different stages of the disease. In early stages of ADPKD, cysts are generated from tubule segments that are perfused by glomerular filtrate [26]. These cysts have a diameter of a few millimeters, below the detection threshold of the present CT scan evaluation. Thus, the “normal” parenchyma identified by CT scan evaluation probably included not only normal nephrons but also nephrons with early cystic changes that precede the development of radiologically detectable cysts. As the cysts enlarge beyond a few millimeters in diameter, they are detected by CT scan. At this stage, about 75% of the cysts irreversibly lose their connections with the original tubule and become isolated sacs [1]. As a consequence, the normal architecture and function of the original tubules are irreversibly lost, with a consequent reduction in functioning nephron mass. At the same time, isolated cysts continue to grow in a process that may accelerate kidney damage through compression and ischemia of contiguous renal parenchyma [26, 27].

In evaluating the results of this short-term trial of somatostatin, the following facts should be kept in mind. First, somatostatin has been reported to depress GFR slightly and reversibly in human subjects [28–32]. Any tendency for improvement in GFR during treatment with somatostatin might be counteracted by this reversible functional effect. Second, the portion of polycystic kidneys identified radiologically as “parenchyma” probably contained many microscopic cysts, as deduced from the histologic examination of such kidneys at postmortem [33]. Third, the ratio of cyst surface to volume is much larger for small cysts than for bigger ones, so that the rates of secretion and reabsorption by the cyst epithelium may be expected to be proportionately greater per unit of cyst volume. It might be predicted, therefore, that inhibition of secretion by cysts would have its first detectable effect on the volume of small cysts. Perhaps this is responsible for the diminution in the “parenchymal” segment of kidney volume in patients treated with octreotide as compared with placebo treatment. It is also possible that the reduction in parenchyma volume observed during somatostatin therapy reflects inhibition of the tubular cell proliferation that precedes cyst development and detachment from the tubuli of origin [34].

This interpretation is consistent with a possible effect of somatostatin on cAMP signaling that goes beyond an effect on fluid secretion. Indeed, evidence based on studies of cyst epithelial cells in vitro points strongly to a role for cAMP in determining the rate of cyst epithelial cell growth and fluid secretion [35], two biologic processes that are of fundamental importance in the expansion of renal cysts. Recent findings that in experimental models of human autosomal-recessive [36] or dominant [37] PKD these biological processes are effectively inhibited by agents that antagonize cAMP production and activity can be taken to suggest that somatostatin treatment may prevent cyst development and growth by directly affecting cell proliferation and apoptosis. Indeed, somatostatin is known to inhibit cAMP generation in Madin-Darby canine kidney (MDCK) cells [38] and in microdissected rat medullary and cortical collecting ducts [39] and to antagonize the effects of vasopressin in the toad urinary bladder [40] and dog collecting dugs [41] in a manner consistent with inhibition of basal and hormone-stimulated adenyl cyclase. Data that cAMP and agonists of adenyl cyclase stimulate the proliferation of epithelial cells derived from ADPKD kidneys provide convincing evidence that cAMP may have a cystogenetic role also in human disease [35] and can be taken to suggest that in our present study the effects of somatostatin therapy were at least in part mediated by the inhibition of cAMP-dependent polycystic kidney cell proliferation [42]. If early enough, these effects, in addition to preventing cyst formation and growth, might preserve the original tubular architecture, which in turn might prevent further loss of tissue and deterioration of renal function over time. The inhibition of compensatory hypertrophy and hyperplasia of residual glomerular/tubular units still not involved in cyst development and growth might also contribute to the reduction in “parenchyma” volume observed during somatostatin therapy and help to explain the slight GFR reduction observed during somatostatin therapy. Octreotide is known to decrease the GFR in healthy individuals [29, 30], as well as in patients with type 1 diabetes [29–31] or liver cirrhosis [32], perhaps by inhibiting the secretion of growth hormone. Such an effect might counteract the tendency to compensatory hyperfiltration that accompanies the glomerular and tubular hypertrophy/hyperplasia of residual functioning nephrons. In the long-term, glomerular hyperfiltration may cause
premature glomerular obsolescence with worsening proteinuria, declining filtration power, and eventual glomerulosclerosis. Total GFR is maintained until progressive parenchymal loss precludes complete compensation. At that point, total GFR begins to fall rapidly by mechanisms no longer dependent on cyst growth, resulting in irreversible kidney failure [33]. Thus, long-term somatostatin treatment might prove renoprotective in patients with ADPKD not only by preventing cyst development and inhibiting tubular secretion, but also by inhibiting the maladaptive events sustained by, and contributing to, progression to nephron loss.

The good safety profile and the marginal reduction in renal growth demonstrated in this short-term study suggest the feasibility of a randomized trial in larger series of ADPKD patients to verify whether long-term somatostatin treatment may eventually provide effective renoprotection. At the present time no treatment that may appreciably affect the relentless progression of the disease to end-stage has been identified. Studies are also needed to assess the effects of somatostatin therapy in the liver cystic disease that so often accompanies ADPKD.

CONCLUSION

In patients with ADPKD somatostatin therapy given for 6 months is safe and may slow renal volume expansion, largely by preventing the growth of the “parenchymal” volume. Whether this effect may prove renoprotective in the long term should be tested in additional trials of larger duration.

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