Case Reports in Nephrology and Urology

Case Rep Nephrol Urol 2014;4:18–24

DOI: 10.1159/000358268
Published online: February 5, 2014

1664–5510/14/0041–0018$39.50/0
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The Use of Lanreotide in Polycystic Kidney Disease: A Single-Centre Experience

S. Treille[a] J.M. Bailly[b] J. Van Cauter[c] F. Dehout[a] B. Guillaume[a]

Departments of [a]Nephrodialysis and [b]Radiology, and [c]Gastroenterology, Charleroi University Hospital, Charleroi, Belgium

Key Words
Lanreotide · Polycystic kidney disease treatment · Somatostatin analogues

Abstract
The secretion of large volumes of fluid into cysts and changes in the structure and mobility of the cilia of the renal tubular epithelium can lead to nephromegaly. This in turn often causes a deterioration of kidney function and arterial hypertension. In recent clinical studies, somatostatin analogues have demonstrated efficacy in isolated polycystic liver disease and, to a lesser extent, in polycystic kidney disease. Since the publication of these clinical studies, several patients have been referred to us for somatostatin analogue treatment. Here, we report our experience with 6 patients who were treated with lanreotide autogel 120 mg every 4 weeks over 6, 12 or 18 months and were longitudinally followed using CT scans without contrast agents, to evaluate the total bilateral kidney volume. We observed a mean decrease in volume of 4%, with mild to moderate side effects.

Introduction

The incidence of autosomal dominant polycystic kidney disease (ADPKD) is estimated to be between 1:400 and 1:1,000 [1]. This disease affects all ethnicities and is transmitted through families in a dominant manner. Two different mutations have been identified in ADPKD: a mutation on chromosome 16 (*PKD* 1), found in 85% of cases, and a mutation on chromosome 4 (*PKD* 2), which is found in 15% of cases [2]. These mutations result in the production of abnormal polycistin-1 and polycistin-2, respectively, both of which cause changes in the structure of the cilia of renal tubular epithelial cells [2]. The consequences of these mutations – cellular proliferation, the secretion of large volumes of fluid and dediffer-

Serge Treille
Nephrology Unit, CHU de Charleroi
Boulevard Paul Janson 92
BE–6000 Charleroi (Belgium)
E-Mail serge.treille@chu-charleroi.be

entiation – together create a favourable climate for the development of cysts. However, the mechanisms underpinning the formation of cysts remain unclear. One major theory supports a continuum of dedifferentiation, maturation and apoptosis [3].

Nephromegaly resulting from ADPKD probably plays a key role in the deterioration of kidney function and in maintaining arterial hypertension. The CRISP study showed that, in ADPKD patients at high risk of renal failure, the kidney volume increased by 6.76 ± 3.78% per year with a parallel decrease in their glomerular filtration rate (GFR) of 5.04 ± 5.86 ml/min/year [4]. In humans, somatostatin receptors in the kidney are expressed in the glomeruli, vasa recta and tubules [5]. Elevated concentrations of cyclic adenosine 3′,5′-monophosphate have been observed in cysts in humans, stimulating the proliferation of epithelial cells and the hypersecretion of intra-cystic fluid [6]. It has been shown that the administration of somatostatin analogues once every 4 weeks, through inhibition of cyclic adenosine 3′,5′-monophosphate, decreases the growth of liver cysts associated with ADPKD and stabilizes the growth of kidney cysts [7–10].

Here, we present 6 cases of ADPKD patients who were treated with lanreotide autogel 120 mg and were longitudinally followed using computerised tomography (CT) scans without contrast agents, to evaluate the total bilateral kidney volume.

Clinical Cases

Methods and Procedures

Six patients received lanreotide autogel 120 mg every 4 weeks over 6, 12 or 18 months in our centre. All patients had kidney function with a GFR >30 ml/min/1.73 m^2 (table 1). No one had diabetes mellitus, symptomatic gallstones or biliary sludge. Women were excluded if they were pregnant, lactating or potentially childbearing without any adequate contraception. Patients with cancer, a major systemic disease or proteinuria >1 g/day were not approached. None of the patients had received previous treatment with a somatostatin analogue, sirolimus or vasopressin antagonist. The potential side effects of the treatment, such as diarrhoea, abdominal pain or pain at the site of the injection and potential vesicular lithiasis, were discussed and were part of the patients' informed consent.

Kidney (and liver if necessary) volume was measured by CT scan before the start of and at regular intervals following treatment with somatostatin analogues, allowing the evaluation of changes in size and volume of the kidney over time. CT scans were performed using 2 multi-detector CT (MDCT) scanners (a 64-slice and 128-slice MDCT; both Siemens). Acquisition parameters were 120 kV and 165 mAs (with automatic exposure control resulting in a 30–40% dose reduction). The rotation time was 0.33 s on the 64-MDCT and 0.30 s on the 128-MDCT, and the minimum thickness was 0.6 mm per slice. Images were taken without contrast of the entire abdomino-pelvic cavity.

Three-dimensional reconstructions were generated at 3-mm intervals and at 1-mm intervals for increased details of the cystic wall, calcifications and lithiases. An automated assessment of the volume was accomplished on the 3-mm slices using volume analysis software (Siemens Corporation), whereby 1 in 3 axial slices were evaluated by tracing the renal contour manually. The software automatically interpolates the contours of the intermediate slices. For the purpose of reproducibility, the contours at the level of the renal sinus followed the narrowest part, excluding the pyelic cavity and vascular structures outside the chosen limits of the sinus. The software displays the volume, expressed in millilitres, for each kidney.

All images were handled by the same operator and compared with the preceding images.

Case Presentations

Patients 1 and 2 were treated for 18 months with deep subcutaneous injections of 120 mg lanreotide autogel (Somatuline® Autogel Injectable) once every 4 weeks. These patients had no cysts in the liver. Patient 1 was a woman, 22 years old at the time of inclusion. She had no significant medical history other than resistant hypertension requiring quadri-therapy including diuretics and angiotensin II receptor blockers. Her kidney function was normal at the start of treatment (table 1). This patient showed substantial improvement, not only in terms of kidney volume (fig. 1a), with a decrease of 18.5% for the left and 13.8% for the right kidney over the 18 months of treatment (equalling a 16% reduction in total kidney volume), but also in terms of blood pressure. Treatment changed from quadri-therapy to mono-therapy with angiotensin II receptor blockers. Patient 2, also treated over 18 months, was a man, 27 years old at the time of inclusion. This patient showed a more modest improvement, with a reduction of 3.7% in total volume after 18 months of lanreotide administration (fig. 1b).

Patients 3 and 4 have been followed for 1 year at our centre; their treatment was ongoing at the time of developing this report. Kidney volume (fig. 2) and estimated GFR levels (table 1) are shown for both patients. Patient 3, a 56-year-old woman (age at inclusion), presented with hypertension and a markedly enlarged kidney, palpable from the anterior abdominal wall. Her CT scan revealed a few cysts with calcified walls. Since no decrease in kidney volume was observed for this patient (the total volume increased by 1%; fig. 2b), we proposed to increase the treatment dose to 180 mg lanreotide once every 4 weeks. Patient 4 was a 47-year-old man. He presented with hypertension and polycystosis of both the liver and the kidney. To date, he has received 12 injections of the somatostatin analogue lanreotide. The total kidney volume of this patient decreased only very slightly during the 1-year follow-up (0.2%). However, the liver volume decreased from 1,305 to 1,226 ml over the same period of time.

The last two patients (patients 5 and 6) in this series, 55 and 33 years of age at the time of treatment initiation, showed reductions of 5.4 and 0.1%, respectively, over a 6-month treatment period. No serious adverse event occurred during the treatment, in particular no cholelithiasis or acute cholecystis. Our patients only complained of pain at the injection site, which is quite different of the findings of the Italian ALADIN study [11], where almost 90% described at least one adverse event.

Body weight and diastolic and mean blood pressure measurements were similar at the beginning and the end of treatment for all 6 patients.

Overall, we observed a mean decrease in total kidney volume of 4% for this series of patients. Serum creatinine levels and estimated GFR levels were within the normal ranges both before and after treatment for all patients (table 1).

Discussion

The use of the somatostatin analogue lanreotide in isolated polycystic liver disease or polycystic liver disease associated with ADPKD has been evaluated in recent clinical studies. Discrete reductions in kidney volume were shown for patients with lesions in both the liver and the kidney. A large clinical study evaluating the effects of lanreotide on kidney volume and GFR in ADPKD patients with polycystic kidney disease is now ongoing in the Nether-

lands. The ALADIN study group [11] has recently published the results of their single-blind, academic, placebo-controlled, randomised study including 75 patients on octreotide for 3 years. They observed a total kidney volume regression after 1 year of treatment, but no significant difference at 36 months on MRI scans.

Animal models suggest that there might be a decrease over time in the response to somatostatin analogue treatment, related to the duration of treatment and the dose administered [8]. Another cause of poor response to treatment could be the downregulation of the ligands, probably by endocytosis, binding the somatostatin receptor following exposure to an analogue [9]. It will thus be of interest to evaluate the results from patient 3, who did not experience a decrease in kidney volume after 12 months of treatment and for whom we increased the dose after 12 months from 120 to 180 mg.

In our cases, we observed better responses to lanreotide in patients with estimated GFR levels >60 ml/min/1.73 m^2 (patients 1, 4 and 5). The patients with creatinine clearance levels corresponding to stage 3 chronic kidney disease or below at treatment initiation had a lesser or poor response to the treatment. This suggests that early therapy with lanreotide in ADPKD patients may be associated with a better treatment response, though this needs to be further evaluated in randomized controlled clinical studies.

Mild to moderate side effects were reported by our patients. These side effects were in line with side effects reported in the literature. We mainly observed flattened stools in the days following the injection and pain at the injection site. Our patients did not develop impaired glucose tolerance, diabetes or gallstones.

In conclusion, the results obtained in this limited series seem encouraging and might offer a new perspective for patients with ADPKD. It is notable that we observed a decrease in volume that persisted over 18 months, though these findings need to be confirmed in larger controlled clinical studies. If these data are confirmed on a larger scale and since lanreotide has an acceptable tolerance profile, this treatment might offer a new strategy for the treatment of ADPKD patients.

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Acknowledgements

We thank Juliette Gray and Adriana Rusu (XPE Pharma and Science, on behalf of IPSEN NV BeLux) for their editorial assistance. Special thanks to Vincent De Ruyter, Medical Advisor at IPSEN NV BeLux, for the review of the manuscript.

Disclosure Statement

All authors declare no conflicts of interest.

Ipsen took on all costs associated with the development and the publication of the present article.

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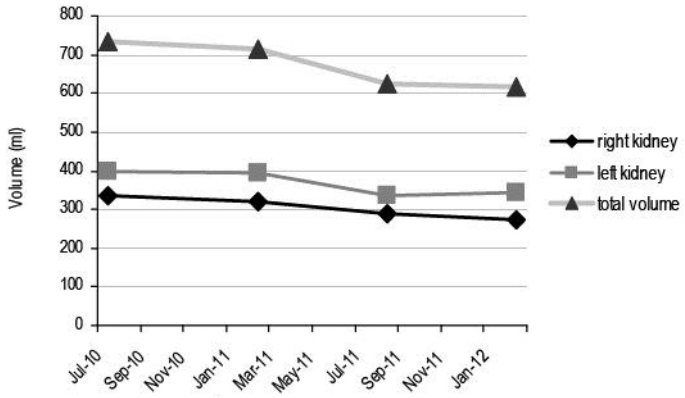
Table 1. Estimated 4-variable MDRD GFR levels (in ml/min/1.73 m²) available during the treatment period

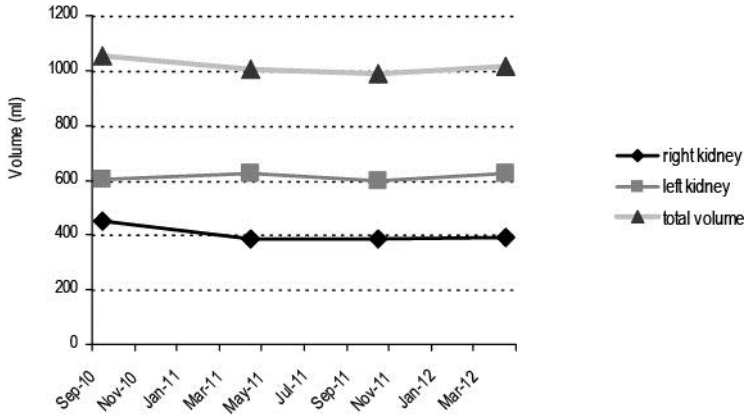
	Date of sample collection	Estimated GFR level
Patient 1	July 2010[a]	102
	December 2010	99.7
	June 2011	96
	January 2012	101
Patient 2	September 2010[a]	62.7
	May 2011	49.6
	January 2012	48.3
Patient 3	May 2011[a]	44
	November 2011	42
	June 2012	35
Patient 4	May 2011[a]	58
	December 2011	61
	May 2012	56

[a] The first readings for each patient were before the start of the treatment.



Date	Kidney Volume (ml)	
	Right	Left
Jul-10	335	398
Feb-11	320	393
Aug-11	288	337
Feb-12	273	343

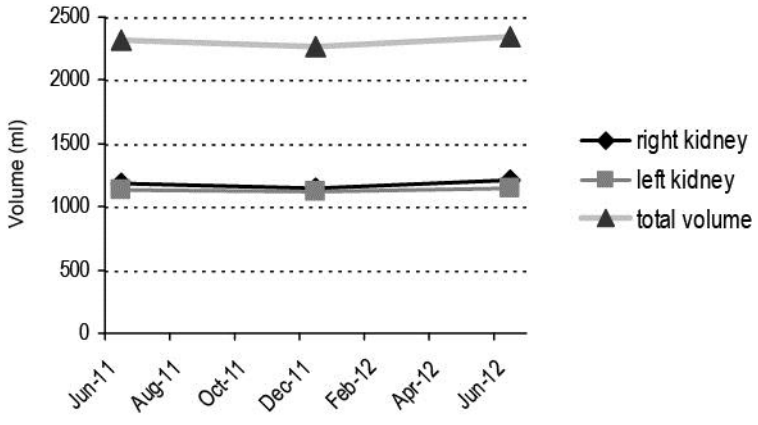
a



Date	Kidney Volume (ml)	
	Right	Left
Sep-10	451 ml	604 ml
Apr-11	383 ml	623 ml
Oct-11	388 ml	599 ml
Apr-12	390 ml	623 ml

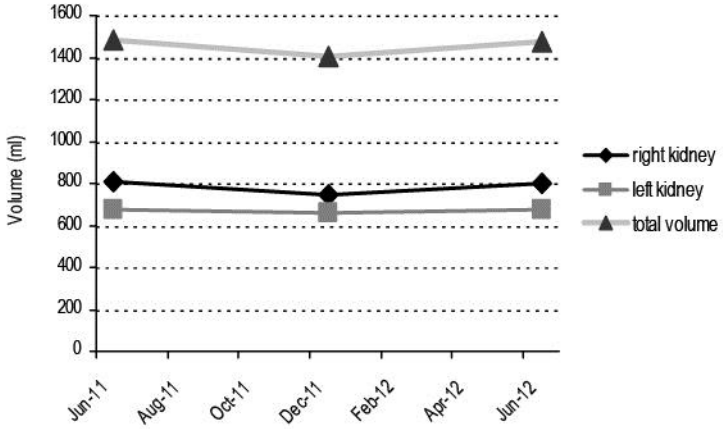
b

Fig. 1. Kidney volume progression in 2 patients treated for 18 months with lanreotide: patient 1, a 22-year-old woman (**a**), and patient 2, a 27-year-old man (**b**).



a

Date	Kidney Volume	
	Right	Left
Jun-11	1188 ml	1130 ml
Dec-11	1148 ml	1114 ml
Jun-12	1205 ml	1145 ml



b

Date	Kidney Volume	
	Right	Left
Jun-11	807 ml	678 ml
Dec-11	745 ml	656 ml
Jun-12	803 ml	675 ml

Fig. 2. Kidney volume progression in 2 patients treated for 12 months with lanreotide: patient 3, a 56-year-old woman (**a**), and patient 4, a 47-year-old man (**b**).