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ALADIN: wish granted in inherited polycystic kidney disease?

Qi Qian and Hai Yan Wang*

Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA (QQ); and Division of Nephrology, Department of Medicine, The First Hospital, Institute of Nephrology, Peking University, Haidian, Beijing 100034, China (HYW)

Autosomal dominant polycystic kidney disease is one of the most common monogenic disorders, occurring in one in every 400–1000 livebirths and characterised by progressive cystic organ enlargement, mainly involving the kidney and liver. Cystic kidney enlargement is correlated with progressive loss of kidney function, leading to kidney failure in about half of affected individuals.¹

The mechanism of cyst growth is complex, involving hyperproliferation of epithelial cells, transepithelial fluid secretion, and pericystic neovascularisation. Evidence suggests that these abnormalities are driven by the accumulation of intracellular cyclic AMP (cAMP),² defects in intracellular calcium homeostasis,³ and hyper-activation of several signalling pathways, including but not limited to MAPK–ERK² and mTOR.⁴

Somatostatin is a naturally occurring (21 aminoacid) peptide inhibitory hormone discovered by Guillemin and Schally in 1973. It has a short half-life (about 3 min) and, through interacting with its receptors (SSTR1–5), modulates circulating concentrations of growth hormone, thyroid-stimulating hormone, pancreatic enzymes, and many gastrointestinal neuropeptides.^{5,6} The SSTRs are expressed in the kidney and liver,⁷ and their activation inhibits cellular cAMP generation and proliferation.

Octreotide is a synthetic octapeptide analogue of somatostatin with a longer half-life (90–120 min) and pharmacodynamic action (8–12 h) when administered subcutaneously. Octreotide-LAR (longacting release) is a formulation of octreotide encapsulated in slowly dissolving polymeric microspheres. It reaches steady-state kinetics when administered intramuscularly every 28 days.⁸ Several preclinical and short-term (up to 1 year) clinical studies show a slowing of kidney and liver cyst growth in autosomal dominant polycystic kidney disease with octreotide-LAR treatment.^{9–11}

In *The Lancet*, Anna Caroli and colleagues¹² present the results of the ALADIN trial (A Long-Acting somatostatin on Disease progression in Nephropathy due to auto-somal dominant polycystic kidney disease), which was a multicentre, randomised, single-blind, placebo-controlled trial with the primary endpoint of change in total kidney volume at 1 year and 3 year follow-up.

why@bjmu.edu.cn.

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79 patients with autosomal dominant polycystic kidney disease (mean age 37 years; mean glomerular filtration rate [GFR] 83.4 mL/min per 1.73 m²) were enrolled at six Italian sites between April, 2006, and May, 2008, and were randomised to octreotide-LAR (30 mg every 28 days, n=40) or placebo (0.9% sodium chloride solution every 28 days, n=39) injections. A significant reduction in the rate of kidney enlargement (measured by MRI) was identified in the octreotide group compared with the placebo group at 1 year (absolute change with octreotide-LAR 46.2 mL [SE 18.2] vs placebo 143.7 mL [26.0]; p=0.032). At 3 years, the kidney volume in the treatment group remained numerically smaller but the difference between the two groups was no longer significant. Following a similar pattern, kidney cyst volume was significantly smaller in the octreotide-LAR group at 1 year (absolute change with octreotide-LAR 33.0 mL [SE 14.7] vs placebo 108.5 mL [18.3]; p=0.017) but at 3 years the difference between the two groups was not significant. A decrease in GFR (measured by iothexol plasma clearance) was more notable at 1 year in the octreotide-LAR group (10.8%) than in the placebo group (9.7%), but, in years 2 and 3, GFR stabilised in the octreotide-LAR group while decreasing steadily in the placebo group.

Adverse effects noted with octreotide-LAR treatment for 3 years were relatively benign. Cholelithiasis and urinary tract infection were rated as severe adverse events. Reduced gallbladder emptying associated with inhibition of intestinal cholecystokinin by somatostatin probably caused cholelithiasis.¹³ Hypoglycaemia, paradoxically, was noted in two patients in the octreotide-LAR group, one of whom was removed from the study.

Because the mutations of *PKD* genes are non-modifiable, the pathological inputs stimulating cyst growth are presumably non-remitting. Thus, any cyst-inhibitory treatment would have to be life-long. Although 20 years of clinical experience with long acting somatostatin show a mild adverse profile, readers should be mindful that the safety data were gathered almost exclusively from patients with cancer, who had hypersecretion of growth hormones, insulin-like growth factors, and gastrointestinal peptides, which are fundamentally different pathological features from those in patients with autosomal dominant polycystic kidney disease, who show no hormonal abnormalities. Whether or not inhibition of these hormones to a subnormal concentration for decades is associated with any untoward effect remains unknown.

Another caveat of the ALADIN trial relates to the efficacy of octreotide-LAR. The cyst inhibitory effect from the treatment was impressive at 1 year. The effect, however, was greatly attenuated by years 2 and 3 despite continuing treatment and, at the end of the study, differences in both kidney volume and cyst volume between the two groups were no longer significant. Such an escape phenomenon is of concern. Incidentally, a loss of responsiveness to octreotide-LAR was noted in treatment of patients with carcinoid syndrome.¹⁴ A potential explanation might be the downregulation of SSTRs.⁶ If true, the initial beneficial effects of octreotide-LAR in autosomal dominant polycystic kidney disease could eventually disappear. Thus, whether the diminished responsiveness to octreotide-LAR in this disorder is lasting warrants further investigation. Up to now, no medical treatment has been shown to reduce cyst growth safely in autosomal dominant polycystic kidney disease. In view of mounting evidence suggesting that cyst growth is probably the outcome of a complicated pathological signalling ensemble, achieving lasting cyst inhibition will probably need

simultaneous or sequential use of several agents. Somatostatin analogues could potentially be useful agents to combat autosomal dominant polycystic kidney disease; however, a longer, multinational, randomised controlled trial with an appropriate sample size is needed.

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Figure 1.
Coloured MRI showing polycystic kidneys (brown)