

# Does extended-release somatostatin slow the growth of renal cysts in autosomal-dominant polycystic kidney disease?

**Original article** Ruggenenti P *et al.* (2005) Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney Int* 68: 206–216

## SYNOPSIS

**KEYWORDS** cyst volume, polycystic kidney disease, somatostatin

### BACKGROUND

Growth of renal cysts is implicated in the progression of autosomal-dominant polycystic kidney disease (ADPKD). Observing stabilization of cyst area in an ADPKD patient with pituitary adenoma who received somatostatin, Ruggenenti *et al.* hypothesized that this agent might have beneficial actions in ADPKD.

### OBJECTIVE

To evaluate the safety of an extended-release somatostatin formulation in patients with ADPKD and impaired kidney function, and its effects on kidney structure and function.

### DESIGN

Adults with clinically and echographically confirmed ADPKD, and serum creatinine  $>106 \mu\text{mol/l}$  ( $>1.2 \text{ mg/dl}$ ) and  $<265 \mu\text{mol/l}$  ( $<3.0 \text{ mg/dl}$ ) if male, or  $>88 \mu\text{mol/l}$  ( $>1.0 \text{ mg/dl}$ ) and  $<265 \mu\text{mol/l}$  ( $<3.0 \text{ mg/dl}$ ) if female, were recruited in a randomized, placebo-controlled, crossover pilot study. Exclusion criteria included other diseases affecting the kidney parenchyma or urinary tract, proteinuria  $>1 \text{ g/24 h}$ , and diabetes. Patients with no ultrasonographic signs of urinary or gallbladder calculi at baseline underwent blood pressure measurement, blood and urine analysis, glomerular filtration rate (GFR) measurement, and contrast-enhanced CT to determine renal and cystic volumes.

### INTERVENTION

Patients were randomized to receive intragluteal injections of long-acting somatostatin 40 mg every 28 days, or placebo, for 6 months. After 6 months, patients switched treatments. Ultrasound, blood pressure and laboratory

evaluations were repeated 2-monthly throughout, and CT and GFR assessments were performed again after each 6-month treatment phase.

### OUTCOME MEASURES

The primary efficacy endpoint was total kidney volume. Cystic volume (including all cysts  $\geq 3 \text{ mm}$  in diameter), parenchymal volume (including normal parenchyma, and parenchyma containing cysts too small to be identified by CT) and GFR were also measured.

### RESULTS

One somatostatin-treated patient and one placebo-treated patient withdrew from the study as a result of developing gallstones and asthenia, respectively. Among the 12 patients included in the analysis (median age 44.5 years, 9 male), baseline mean total kidney volume was 2,435 ml (range 1,498–4,294 ml), of which 65% comprised cysts on average (range 52–86%). After 6 months on somatostatin, kidney volume increased by 71 ml ( $P < 0.05$ ) compared with an increase of 162 ml ( $P < 0.01$ ) after 6 months on placebo. Total kidney volume increased by a significantly lower percentage during somatostatin treatment than during placebo administration (+2.2% vs +5.9%;  $P < 0.01$ ). There was a trend towards a smaller increase in cystic volume during somatostatin treatment than during placebo administration (+3.0% vs +5.6%). A nonsignificant decrease in parenchymal volume of 4.4% was seen after somatostatin treatment and a nonsignificant increase in parenchymal volume of 2.5% occurred after placebo. Somatostatin was well tolerated. Self-resolving watery diarrhea occurred in 3 patients. There were no significant changes in blood pressure, GFR, serum creatinine or albuminuria during placebo or somatostatin treatment.

### CONCLUSION

In patients with ADPKD and mild to moderate renal insufficiency, long-acting somatostatin is well tolerated and associated with slower increase in kidney volume than placebo.

## COMMENTARY

## Jared J Grantham

It is generally accepted that the relentless enlargement of cysts derived from renal tubules seen in patients with polycystic kidney disease (PKD) can largely be attributed to the proliferation of mural epithelial cells and the transport of fluid into the cavities generated by accelerated epithelial cell growth.<sup>1</sup> *In vitro* evidence indicates that this cell growth and transepithelial secretion of fluid is under the control of cyclic AMP. More recent studies in four animal models of PKD revealed that renal enlargement due to cyst formation can be slowed by reducing cyclic AMP production with an inhibitor of the arginine vasopressin V2 receptor.<sup>1–3</sup>

Ruggenti *et al.* report the first prospective, placebo-controlled trial designed to slow the progression of renal enlargement in patients with ADPKD. A long-acting somatostatin analog was administered to 12 patients in this crossover study, with the intention of inhibiting cyclic AMP production within renal cells, thereby reducing the rates of cell proliferation and fluid secretion. Contrast-enhanced CT was used to monitor the effects of somatostatin on cyst and kidney volume.

Somatostatin reduced the rate of total kidney volume increase over a 6-month interval by more than 60% compared with placebo treatment in the same subjects. The absolute change in kidney volume was modest; nonetheless, the result will be music to the ears of PKD patients and researchers who have waited patiently for more than 20 years since the goal of treating these disorders was first established by the Polycystic Kidney Disease Foundation.

The crossover design used in the Ruggenti *et al.* trial is well-suited to pilot studies of this type. The paired statistical analysis reveals meaningful drug effects with far fewer subjects than would normally be required. Moreover, the pilot study concept seems appropriate for ADPKD, a condition for which increasing numbers of candidate treatments are already on the shelves or in the development pipeline. The

pilot study makes it possible to select relatively potent agents of promise for large-scale clinical trials, thereby reducing the costs of bringing exciting candidates from the laboratory to the bedside. This should be welcomed by the pharmaceutical industry: drug companies have been slow to develop treatments for ADPKD because of the long course of the disease, during most of which the patient enjoys normal renal function.

The renal cysts observed in patients with ADPKD actually form within the kidney tubules, becoming so numerous that they cause the organs to enlarge, often grotesquely. Cyst and kidney enlargement reflects progression of the disease from birth, and much morbidity attributable to the cysts, such as hypertension, hemorrhage, and pain, occurs long before the development of renal insufficiency. Technological advances now allow cyst and kidney volumes to be accurately measured in individual patients using CT and MRI.<sup>4</sup> As illustrated in the current study, the course of PKD can therefore be determined within fairly short periods of time, if the kidneys show relatively rapid rates of growth.

Breakthrough might be too strong a word to describe the present study, but Ruggenti *et al.* have certainly made a large crack in the wall that has hitherto prevented effective therapy for ADPKD.

## References

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## Competing interests

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## PRACTICE POINT

Somatostatin merits a full-scale clinical trial in autosomal-dominant polycystic kidney disease; in the short term, it can be considered for patients with intractable pain and rapidly expanding kidneys