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ORIGINAL ARTICLE

Safety study of somatostatin analogue octreotide for autosomal dominant polycystic kidney disease in Japan

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Abstract
Background The total kidney volume (TKV) and total liver volume (TLV) increase and renal function decreases progressively in patients with autosomal dominant polycystic kidney disease (ADPKD). Somatostatin analogues, such as octreotide, reduce these increases in TKV and TLV. The aim of this study was to examine the safety of the short-term administration of octreotide long-acting release (octreotide-LAR) in a small number of cases.
Methods Four ADPKD patients with an estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 m^2, TKV $> 1{,}000$ mL, and TLV $> 3{,}000$ mL were enrolled. Two 20-mg octreotide-LAR intramuscular injections were repeated every 4 weeks for 24 weeks. Laboratory and clinical assessments were repeated every 4 weeks, and TKV and TLV were measured by magnetic resonance imaging before and after the study.
Results In the laboratory tests, there was no abnormal variable except for a significant decrease of alanine aminotransferase. The means of TKV and TLV decreased from 2,007 to 1,903 mL and from 9,197 to 8,866 mL, respectively, but the changes were not significant. eGFR did not change significantly. Adverse events involved loose stools in two patients, as well as injection site granuloma and abdominal pain in one patient each, which resolved spontaneously.
Conclusion Octreotide-LAR may be safe and effective for preventing TKV and TLV increases (UMIN000009214).

Keywords Autosomal dominant polycystic kidney disease (ADPKD) · Somatostatin · Octreotide · Kidney volume · Liver volume

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic renal disorder. Multiple cysts develop in the kidney, and end-stage renal failure eventually develops in half of the patients by their sixties [1–3]. Polycystic liver disease is the most frequent extrarenal manifestation, and hepatic cyst enlargement progresses as the age advances [4, 5]. The quality of life is markedly impaired due to the psychological burden brought about by inheritable disease, as well as the symptoms caused by the kidney and liver enlargement and deteriorated kidney function.

ADPKD is a result of mutations in Pkd1 or Pkd2, genes encoding polycystin-1 (PC-1) and polycystin-2 (PC-2), respectively. PC1 and PC2 are integral membrane proteins working as nonselective calcium channels that are normally localized in primary cilia. When Pkd genes are

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mutated, the absence of their protein products results in ciliary dysfunction and cyst formation in the kidney [6, 7] and liver [8, 9]. The physiologic function of primary cilia in the kidney is to detect tubular fluid flow and convert mechanosensation into intracellular Ca^{2+} influx [10, 11]. Cholangiocyte cilia also act as mechanosensors that monitor luminal bile flow and convert stimuli into intracellular Ca^{2+} influx [9].

Increased renal and liver concentrations of 3′–5′-cyclic adenosine monophosphate (cAMP) are common in animal models of polycystic kidney disease [12, 13]. The elevated cAMP could be directly related to changes in intracellular Ca^{2+} homeostasis by stimulation of the Ca^{2+}-inhibitable adenylyl cyclase and inhibition of phosphodiesterase [14]. cAMP has a downstream effector protein kinase A (PKA) that is responsible for the hyperproliferation of epithelial cells both of renal cysts from patients with ADPKD [15, 16] and of hepatic cysts from PCK rats [13].

Arginine vasopressin (AVP) stimulates the production of cAMP and cell proliferation in human ADPKD cells [17]. Tolvaptan, an AVP-V2-receptor (V2R) antagonist, decreases cAMP production and attenuates cyst development in animal models [18, 19], and reduces total kidney volume (TKV) enlargement and kidney function deterioration in ADPKD patients [20, 21]. Somatostatin, acting on somatostatin2 (SST2) receptors, inhibits secretin-induced cAMP generation in cholangiocytes of animal models of polycystic liver disease [22], and inhibits vasopressin-induced cAMP generation in collecting ducts by its effect on Gi protein-coupled receptors [23–25].

Based on the findings described above, prospective clinical studies were conducted to examine the effects of somatostatin analogues on ADPKD [26–29]. In the present short-term and uncontrolled preliminary study, the safety of octreotide long-acting release (octreotide-LAR) was re-examined, and its effects on TKV and TLV were evaluated. The present study required regulatory approval to plan a long-term, placebo-controlled octreotide-LAR efficacy study in patients with ADPKD.

Materials and methods

Patient selection

Four patients with ADPKD were recruited from Kyorin University Hospital. Men and women aged between 20 and 60 years, with a clinical and imaging diagnosis of ADPKD according to Pei et al. [30] criteria, estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2 or higher as calculated by the Japanese coefficient of modified isotope dilution mass spectrometry-modification of diet in renal disease (IDMS-MDRD) study [31], TKV of 1,000 mL or higher, and total liver volume (TLV) of 3,000 mL or higher as measured by magnetic resonance imaging (MRI) [32] were eligible. We excluded female patients who were pregnant or lactating and patients with diabetes mellitus, symptomatic cholelithiasis, planned surgery during the study period, and other factors confounding the study.

The study conformed to the principles of the Declaration of Helsinki. The protocol was approved by an institutional review board (No. 521) and registered in the University Hospital Medical Information Network (UMIN) (UMIN000009214) in Japan. All participants gave written informed consent.

Octreotide-LAR administration and laboratory test

After receiving informed consent, vital signs, physical examination results, and laboratory blood test findings were assessed before administrating a subcutaneous test dose of 100 μg of octreotide-LAR. Participants received two 20-mg intramuscular injections of octreotide-LAR 24 h after test injection and every 4 weeks thereafter for a total of six times. Laboratory blood tests were repeated 4 weeks after each injection of octreotide-LAR.

Kidney function was estimated with the eGFR using two equations. eGFR(Eq_{cr}) was calculated using the Japanese coefficient of IDMS-MDRD Study [31]. eGFR($Eq_{cr\text{-}cys}$) is a Japanese modification of MDRD with cystatin C [33, 34]:

$$\mathrm{eGFR}(\mathrm{Eq_{Cr}}) = 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-0.287} \times 0.739 \text{ (if female)}$$

$$\mathrm{eGFR}(\mathrm{Eq_{Cr-Cys}}) = 92 \times \mathrm{CysC}^{-0.575} \times \mathrm{Cr}^{-0.670} \times 0.995^{\mathrm{Age}} \times 0.784 \text{ (if female)}$$

Gall-bladder stones were surveyed using ultrasonography before and after the study.

Organ volume measurements

Kidney and liver volumes were measured using MRI or computed tomography (CT) within 4 weeks before the initial test doses and after the last injection. MRI was used for three patients and CT was used for TLV measurement in one patient whose large liver prevented precise MRI measurement. The non-contrast MRI acquisition protocol and kidney volume measurement are reported elsewhere [32].

For measurement of the liver volume, the coronal T1-weighted liver MR images were obtained by 3D-fast field echo (3D-FFE) with a slice thickness of 5 mm. All images were transferred to a 3D workstation (AZE Virtual Place Lexus 64, AZE Ltd. Tokyo, Japan). The entire liver border was segmented manually. After extracting the 3D liver image, the volume was calculated automatically with the 3D station. The correlation coefficients between the two

Table 1 Data of participants

Patient	Sex	Age (years)	Height (cm)	BW (Kg)
1	Male	47	177	70
2	Male	45	174	64
3	Female	45	153	48
4	Female	41	152	48

BW body weight

volume measurements of the 12 liver samples determined by a single reader and two different readers blinded to other data were 0.9998 and 0.9995, respectively. The mean % difference between the two measurements by a single reader and two different readers were 0.76 ± 2.78 and 0.13 ± 3.83 % (SD), respectively.

Height-adjusted TKV and TLV (ht-TKV and ht-TLV, respectively) were used to minimize the body size factor [35].

Statistical analyses

Analyses were performed using SAS 10 for Windows. Data are expressed as the mean ± standard deviation. Two-sided $p < 0.05$ was considered significant.

Results

Patients

Between March and October 2013, four patients with ADPKD attending our clinic were enrolled. The baseline data of the participants are presented in Table 1.

Safety

Treatment was well tolerated in all patients. There was no serious adverse event. Loose stools, abdominal pain, and granuloma at the injection site were transient, self-limiting, and spontaneously resolved. The majority of these adverse events appeared with the early injections including the subcutaneous test doses (Table 2).

The enlarged cystic kidney and liver obscured the evaluation of gall-bladder stones with ultrasonography. However, no symptom suggesting cholelithiasis was reported by the patients.

The effects of octreotide-LAR on clinical and laboratory data

In Table 3, comparisons of the clinical and laboratory data between the baseline and final measurements are summarized. TKV, TLV, hemoglobin, hematocrit, and γ-GTP tended to decrease (non-significant). Alanine aminotransferase (ALT) decreased significantly. Fasting blood sugar and hemoglobin A1c tended to increase (non-significant). The individual data on TKV, TLV, and renal functions before and

Table 2 Adverse events

Patient	Loose stools[a]	Granuloma[b]	Abdominal pain[a]
1	2 (T and 1)	1 (2)	0
2	0	0	0
3	2 (T and 4)	0	0
4	0	0	1 (1)
Total	4	1	1

Number in parenthesis is the time when the adverse event occurred on consecutive injection (one test and six regular injections)

T test dose injection

[a] Loose stools and abdominal pain are self-resolving

[b] Granuloma is an injection site granuloma with pain, which resolved spontaneously within 2 months

Table 3 Comparison between baseline and final data

	Baseline	Final	*p*
Syst. BP (mmHg)	127.3 ± 9.3	127.3 ± 9.9	1.00
Diast. BP (mmHg)	82.3 ± 13.3	81.3 ± 9.2	0.67
TKV (mL)	2,007 ± 701	1,903 ± 694	0.31
TLV (mL)	9,197 ± 5374	8,866 ± 5292	0.13
eGFR(Eq_{cr}) (mL/min/1.73 m^2)	55.0 ± 9.7	55.8 ± 12.0	0.79
eGFR($Eq_{cr\text{-}cys}$) (mL/min/1.73 m^2)	59.7 ± 13.7	61.3 ± 15.3	0.50
FBS (mg/dL)	93.3 ± 12.7	94.8 ± 12.0	0.25
HbA1c (NGSP) (%)	5.75 ± 0.61	5.88 ± 0.51	0.34
Hb (g/dL)	13.3 ± 1.3	12.7 ± 2.2	0.25
Hct (%)	41.0 ± 4.0	38.2 ± 7.1	0.17
Cr (mg/dL)	1.06 ± 0.26	1.05 ± 0.24	0.81
Na (mEq/L)	140.5 ± 1.7	140 ± 1.4	0.39
Alb (mg/dL)	4.65 ± 0.1	4.38 ± 0.31	0.19
γ-GTP (IU/L)	191.0 ± 149.3	148.8 ± 109.8	0.13
AST (IU/L)	24.0 ± 3.6	19.5 ± 2.1	0.073
ALT (IU/L)	24.8 ± 6.7	15.3 ± 6.4	0.033

Data are presented as the mean ± SD. *p* values were calculated using the paired-*t* test. Final data are at 4 weeks after the last injection of octreotide-LAR

Syst. BP systolic blood pressure, *Diast. BP* diastolic BP, *TKV* total kidney volume, *TLV* total liver volume, *eGFR*(Eq_{cr}) estimated GFR using the Japanese modification of IDMS-MDRD, $eGFR(Eq_{cr}) = 194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female), *IDMS* isotope dilution mass spectrometry, *MDRD* modification of diet in renal disease, *eGFR*($Eq_{cr\text{-}cys}$), estimated glomerular filtration rate using the Japanese modification of MDRD with cystatin C incorporated, $eGFR(Eq_{cr\text{-}cys}) = 92 \times SCystC^{-0.575} \times SCr^{-0.670} \times 0.995^{Age} \times 0.784$ (if female), *FBS* fasting blood sugar, *HbA1c* (*NGSP*) hemoglobin A1c national glycohemoglobin standardization program, *Hb* hemoglobin, *Hct* hematocrit, *Cr* Creatinine, *Na* plasma sodium, *γ-GTP* γ-glutamyltranspeptidase, *AST* asparate aminotransferase, *ALT* alanine aminotransferase

Table 4 Individual data

Patient	TKV		TLV		eGFR(Eq_{Cr})		eGFR($Eq_{Cr\text{-}Cys}$)		Cr	
	Baseline	After	Baseline	After	Baseline	After	Baseline	After	Baseline	After
1	2,467	2,570	12,011	11,246	47.3	54.1	52.8	58.6	1.33	1.17
2	2,587	2,271	15,373	15,210	53.2	51.4	50.2	50.7	1.21	1.24
3	1,924	1,789	4,412	4,376	50.3	44.7	55.7	52.1	0.96	1.07
4	1,049	980	4,992	4,630	69.1	73.0	80.0	83.6	0.74	0.70
Mean	2,007	1,903	9,197	8,866	55.0	55.8	59.7	61.3	1.06	1.05
SD	701	694	5,374	5,292	9.7	12	13.7	15.3	0.26	0.24
p value	0.31		0.13		0.79		0.50		0.81	

p values were calculated using the paired-*t*-test

TKV total kidney volume, *TLV* total liver volume, *eGFR*(Eq_{cr}) estimated GFR using the Japanese modification of IDMS-MDRD, $eGFR(Eq_{cr}) = 194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female), *IDMS* isotope dilution mass spectrometry, *MDRD* modification of diet in renal disease, *eGFR*(*Eqcr-cys*) estimated glomerular filtration rate using the Japanese modification of MDRD with cystatin C incorporated, $eGFR(Eqcr\text{-}cys) = 92 \times SCystC^{-0.575} \times SCr^{-0.670} \times 0.995^{Age} \times 0.784$ (if female), *Cr* Plasma creatinine

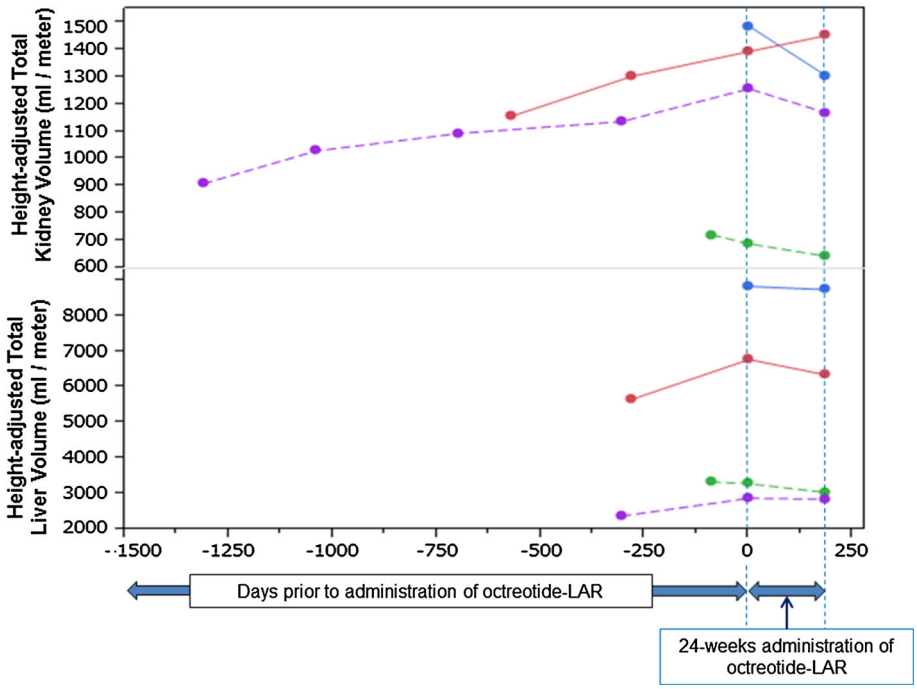

Fig. 1 Changes in the height-adjusted total kidney volume (ht-TKV) and height-adjusted total liver volume (ht-TLV) before and after octreotide-LAR administration. For some patients, the organ volumes measured prior to the study are plotted. *Solid line* represents males, and *dotted line* represents females. Changes between before and after are non-significant ($p = 0.31$ and $p = 0.13$ for ht-TKV and ht-TLV, respectively)

after octreotide-LAR injections for 24 weeks are presented in Table 4.

Figure 1 illustrates changes of ht-TKV and ht-TLV during the study period. In a few cases, available data from the pre-study period have been added. The changes of $eGFR(Eq_{cr})$ and $eGFR(Eq_{cr\text{-}cys})$ were non-significant during the 24 weeks (Fig. 2).

Discussion

Four randomized, placebo-controlled clinical studies, which examined the safety and efficacy of somatostatin analogues, octreotide-LAR, or lanreotide, in ADPKD patients have been reported [26–29]. The open-label or observational extension studies and post hoc analysis related to these studies were added [36–38]. In these studies, octreotide-LAR and lanreotide were well tolerated overall, and most participants completed the studies. Self-resolving abdominal pain, loose stools, and flatulence are common in the first few days after the initial injection. Other adverse events, including injection-site granuloma and pain, cholelithiasis, steatorrhea, weight loss, and, rarely, hair loss, are described. The present preliminary study showed the safety of octreotide-LAR injection for ADPKD patients. This study, which was consistent with

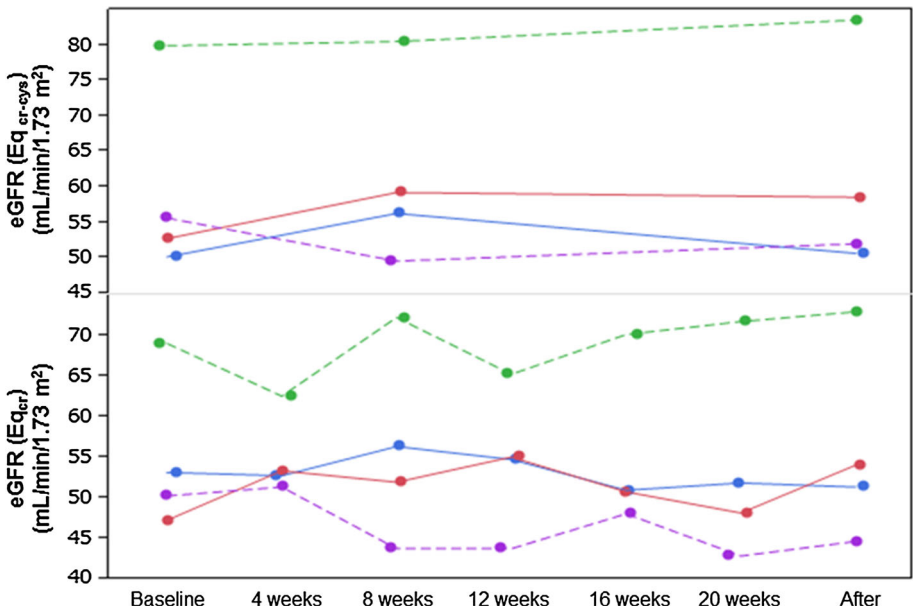

Fig. 2 Changes in the estimated glomerular filtration rate (eGFR) during the 24 weeks of the study. $eGFR(Eq_{cr})$ is calculated using a Japanese modification of IDMS-MDRD, $eGFR(Eq_{cr}) = 194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female), *IDMS* isotope dilution mass spectrometry, *MDRD* modification of diet in renal disease, $eGFR(Eq_{cr\text{-}cys})$ calculated using a Japanese modification of MDRD with cystatin C (SCystC) incorporated, $eGFR(Eq_{cr\text{-}cys}) = 92 \times SCystC^{-0.575} \times SCr^{-0.670} \times 0.995^{Age} \times 0.784$ (if female). *Solid line* represents male, and *dotted line* represents females. Changes between the baseline and after are non-significant ($p = 0.50$ and $p = 0.79$ for $eGFR(Eq_{cr\text{-}cys})$ and $eGFR(Eq_{cr})$, respectively)

previous studies, was required for regulatory approval in order to plan a placebo-controlled clinical trial.

It is interesting that the red cell count and hemoglobin concentration were significantly lower in participants in the octreotide-LAR group than in those in the placebo group in the first year, but the differences disappeared at the 3-year follow-up [29] because a tendency for the hematocrit and hemoglobin to decrease was observed in the present study. The significant decrease of ALT in the present study has not been reported in previous studies, and this may become non-significant with an increase in the subjects.

Generally, somatostatin analogues halted kidney and liver volume increases, at least within 1 year. In an octreotide extension study, the effects on kidney and liver growth rates (% per year) reduced from the first to second year (from −4.95 to −0.77 %/year in liver volume and from 0.25 to 6.49 %/year in kidney volume, statistical analysis not available) [28, 38]. The absolute change in TKV from the baseline was significant between octreotide-LAR and placebo in the first year (46.2 vs. 143.7 mL, respectively, $p = 0.032$), but not significant at 3 years (220.1 vs. 454.3 mL, respectively, $p = 0.23$) [29]. The long-term effects of somatostatin analogues on kidney and liver volume increases remain unclear.

Significant effects on GFR were not observed in the short-term studies in less than 1 year. In the 3-year octreotide-LAR study, beneficial effects on the measured GFR were observed compared to the placebo group between 1 and 3 years (−2.28 vs. −4.32 mL/min per 1.73 m^2 per year, respectively, $p = 0.027$), but the difference was non-significant between 0 and 3 years ($p = 0.13$) [29]. This discrepancy is explained by the acute hemodynamic effects of octreotide, which is known to acutely decrease GFR in healthy and diseased individuals by hemodynamic mechanisms that are probably mediated by inhibited growth hormone secretion [39]. The long-term effect of octreotide on GFR remains unclear, and longer and larger clinical studies are needed to draw a conclusion.

In conclusion, from the present and previous studies, octreotide-LAR is well tolerated overall, and most participants completed the studies. On facing the commencement of the clinical application of tolvaptan in Japan, the use of somatostatin analogues with tolvaptan might bring about additional beneficial effects to prevent disease progression, and such a clinical study is awaited for ADPKD patients.

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Conflict of interest Eiji Higashihara is a member of the Scientific Committee of TEMPO study of Otsuka Pharmaceutical Co. and received a grant from Otsuka Pharmaceutical Co. Kikuo Nutahara

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