Somatostatin in renal physiology and autosomal dominant polycystic kidney disease

A. Lianne Messchendorp¹, Niek F. Castelein², Esther Meijer¹ and Ron T. Gansevoort¹; on behalf of the DIPAK Consortium investigators*

¹Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands and
²Department of Urology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence and offprint requests to: Ron T. Gansevoort; E-mail: R.T.Gansevoort@umcg.nl

*DIPAK Consortium investigators: Joost P. Drenth, Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; Johan W. de Fijter, Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands; Dorien J.M. Peters, Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands; Folkert W. Visser, Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; Jack F. Wetzels, Department of Nephrology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; Robert Zietse, Department of Nephrology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cyst formation, leading to growth in kidney volume and renal function decline. Although therapies have emerged, there is still an important unmet need for slowing the rate of disease progression in ADPKD. High intracellular levels of adenosine 3',5'-cyclic monophosphate (cAMP) are involved in cell proliferation and fluid secretion, resulting in cyst formation. Somatostatin (SST), a hormone that is involved in many cell processes, has the ability to inhibit intracellular cAMP production. However, SST itself has limited therapeutic potential since it is rapidly eliminated in vivo. Therefore analogues have been synthesized, which have a longer half-life and may be promising agents in the treatment of ADPKD. This review provides an overview of the complex physiological effects of SST, in particular renal, and the potential therapeutic role of SST analogues in ADPKD.

Keywords: ADPKD, cAMP, renal physiology, somatostatin, somatostatin analogues

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, with a prevalence of 3–4/10 000 in the general population [1]. ADPKD is characterized by progressive development and growth of numerous renal cysts. This eventually leads to end-stage renal disease in 70% of affected patients at a median age of 58 years. An important extrarenal manifestation is progressive cyst formation in the liver, with a radiological prevalence of 95% by the age of 35–45 years, which leads to symptoms in ~20% of cases [2, 3]. Symptoms in patients with polycystic liver disease (PLD) arise from the enlarged intra-abdominal volume and include abdominal distension, early satiety, herniations, dyspnoea and pain. In a limited number of affected subjects, liver transplantation is necessary [4].

For a long time there were no therapies to slow the rate of disease progression in ADPKD. In the last two decades, however, novel insight into the pathophysiology of ADPKD has led to the discovery of possible targets for treatment. One of these targets is adenosine 3',5'-cyclic monophosphate (cAMP), which is elevated in ADPKD due to disrupted intracellular calcium homeostasis and results in progressive cyst formation in both kidneys [5]. Therapeutic agents that interfere in this pathway can possibly attenuate ADPKD disease progression. The vasopressin V2 receptor antagonist tolvaptan, which down-regulates cAMP, is effective in the treatment of ADPKD [6, 7]. However, the effect of tolvaptan seems limited to renal tubular cells in the distal nephron and collecting duct, which express the V2 receptor. Cysts originating from other nephron segments as well as liver cysts will probably not be affected, although a recent experimental study has suggested that vasopressin V2 receptors are present on biliary cells [8]. However, it has not been shown that tolvaptan affects liver volume in ADPKD. Moreover, aquaretic
side effects limit widespread clinical use of this drug. Therefore there is still an unmet need for new therapies to slow disease progression in ADPKD.

Somatostatin (SST) is a hormone that is involved in many cell processes and directly and indirectly inhibits cAMP production in various tissues, including liver and kidney. SST analogues therefore have a potential role in the treatment of ADPKD for the renal as well as the hepatic phenotype. Studies about SST and its complex signalling pathway mainly date from the 1980s and 1990s. This review provides a summary of the role of SST and SST analogues in physiology, with a focus on the renal effects, and in the pathophysiology of ADPKD. The hepatic effects of SST have recently been reviewed elsewhere [9].

HISTORY OF SST

Somatostatin (SST or SRIF) was first discovered in 1968 by Krulich et al. [10] as a growth hormone–inhibiting factor produced by the hypothalamus. A year later, Hellman and Lernmark [11] found an insulin-inhibiting factor produced by the pancreas. In 1973, Brazeau et al. [12] concluded that these phenomena were caused by the same hormone: SST. After its discovery, subsequent studies revealed that SST is more widely produced throughout the body and induces a broad spectrum of biological effects, but mainly inhibitory.

THE PHYSIOLOGY OF SST

SST

SST is synthesized as part of a large precursor protein, preprosomatostatin (preproSST), which is rapidly processed into prosomatostatin (proSST). This prohormone is enzymatically processed mainly at the C-terminal segment to generate two bioactive forms, SST-14 and SST-28 (Figure 1) [13]. ProSST can also be cleaved at other sites, which creates four more cleavage products, but whether these latter cleavage products have a physiological function remains uncertain [14].

Secretion of SST

SST is produced by different cell types. Most SST-producing cells are found throughout the central and peripheral nervous systems, as well as in the pancreas and gastrointestinal tract. SST-producing cells are also found, although in smaller numbers, in other organs, including the kidney. About 65% of the total body SST is derived from the gastrointestinal tract, 25% from the central nervous system, 5% from the pancreas and 5% from the remaining organs [15]. Secretion of SST is either stimulated or inhibited by a broad spectrum of agents, including ions, nutrients, peptides, neurotransmitters, hormones, growth factors and cytokines. Some of these agents exert common effects on SST cells at different locations, whereas others appear to induce tissue selective effects. For example, nutrients, like glucose, stimulate SST secretion by δ-cells of the pancreas but inhibit SST secretion by cells of the hypothalamus [15].

SST receptors and their activation

SST can act on multiple cellular targets via a family of five receptors: SST receptor (SSTR) 1–5 [15]. The SST receptor subtypes are more or less of equal size and consist of seven helical transmembrane domain, G protein-coupled receptor proteins. Typically, more than one receptor subtype is expressed in a single organ. All receptor subtypes have nanomolar affinity for SST-14 and SST-28, but SSTR1–4 have higher selectivity for SST-14, whereas SSTR5 has a higher selectivity for SST-28 [13].

Ligand binding to these receptors generally results in three effects: inhibition of secretion, inhibition of cell proliferation and induction of apoptosis. Ligand binding to any of the five receptor subtypes first results in activation of the inhibitory G-protein (Gi), followed by modulation of multiple second messenger systems including but not limited to receptor coupling to adenyl cyclase, receptor coupling to K⁺ channels, receptor coupling to Ca²⁺ channels, receptor coupling to protein phosphatases, receptor coupling to exocytotic vesicles and receptor coupling to the mitogen-activated protein kinase pathway. Which second messenger is altered is dependent on the tissuespecific distribution of ligands, receptor subtype and tissue localization of the receptors. For instance, SSTR2–5 are coupled to K⁺ channels, SSTR1 and -2 are coupled to voltage-dependent Ca²⁺ channels, SSTR2 and -5 are coupled to phospholipase C and SSTR1 is coupled to a Na⁺/H⁺ exchanger [16]. As a joint effect, all receptor subtypes inhibit adenyl cyclase and cAMP production.

As SST is produced at sites where the different receptors are expressed, it is suggested that SST elicits its action especially in an autocrine/paracrine manner. However, circulating levels of SST derived from the gastrointestinal tract modulate insulin release, thereby eliciting a true endocrine effect [17, 18]. SST receptor activation therefore involves auto-, para- as well as endocrine mechanisms.

Although the acute administration of SST produces a large number of inhibitory effects, the initial response diminishes with continued exposure to the peptide. The ability of SST receptors to regulate their responsiveness to agonist-specific stimulation typically involves receptor desensitization due to uncoupling of G proteins, as well as receptor internalization and receptor degradation. This process is dependent on receptor subtype, exposure time, ligand concentration and heterologous regulation through other signalling systems [19]. The phenomenon of receptor desensitization is important for treatment with SST (see below).

Metabolism of SST

SST-14 and SST-28 are rapidly metabolized in vivo by cleavage through amino peptidases in blood and tissues. Experiments
with infusion of SST indicate that the liver and kidneys are the main sites of elimination of the molecule (37 and 32.7%, respectively). The remaining 30% of elimination is attributed to the lungs, pancreas and blood, which together result in a metabolic clearance rate of ~30 mL/kg/min and consequently a very short plasma half-life of 1–3 min in vivo [13].

Renal localization of SST-producing cells and SST receptors

As mentioned above, SST-producing cells are also found in the kidney. In vitro studies have shown, for instance, that SST is secreted by mesangial cells and proximal tubular cells. Secretion can be stimulated by cAMP and inhibited by epidermal growth factor and hydrocortisone [20, 21]. Since SST is known to be an endogenous inhibitory regulator, it is suggested that this renal-derived SST modulates mesangial and proximal tubular cell growth and function after binding to renal SSTRs.

There have only been a few studies investigating the renal localization of SSTRs. These studies have shown that mainly SSTR1, -2 and -5 are expressed, especially in the distal tubules [22, 23]. However, a more recent study found positive staining for all receptor subtypes throughout the tubular system, except in the collecting duct [24]. Our study group also investigated renal SSTR localization. We observed SSTR2 expression mainly in distal tubules and collecting ducts in mice, which was in agreement with mRNA expression. In humans, we found conflicting data for immunostainings and mRNA expression [25]. Unfortunately, it is difficult to compare human studies since most studies focus on only very small sections of the kidneys and/or different antibodies were used, sometimes with distinct antigen specificity for the SSTRs. It is important to know which SSTR subtypes are expressed across the various segments of the nephron segments for therapy with SST analogues, which will be discussed later. The renal localization of SSTRs therefore warrants further research.

Effect of SST pathway activation in renal physiology

As mentioned above, binding of SST with SSTRs can activate pathways that can modulate renal cell function and growth. Since renal cells both secrete SST and express SST receptors, SST probably modulates renal cell function and growth in an autocrine/paracrine manner. This theory is supported by the fact that although all SSTRs have nanomolar affinity for biologically active SST (SST-14 and SST-28), systemic fasting plasma SST concentrations have a range that is 100- to 1000-fold lower, that is, between 0.008 and 0.02 nM, which is equivalent to 14–32.5 pg/mL [13]. These very low concentrations are assumed to not reach the threshold to activate SSTRs in the kidney. As SST is partly eliminated by the kidney, it should be stated that filtered SST could theoretically reach higher concentrations in (pre)urine and in this way potentially modulate downstream tubular function.

Activation of SST receptors causes inhibition of the release of aldosterone and renin [26, 27]. Multiple studies have suggested that SST is also involved in renal water handling and can inhibit the proliferation of renal cells [28, 29]. Furthermore, SST causes glomerular vasoconstriction, resulting in decreased renal blood flow and consequently a reduction of the glomerular filtration rate (GFR) [30]. These physiological processes are probably all, or at least partly, a result of the ability of SST to inhibit renal cAMP production [31, 32]. Interestingly, one of the pivotal detrimental factors in the pathophysiology of ADPKD are elevated levels of cAMP. Theoretically, SST and related agonists therefore have the potential to induce a therapeutic effect in ADPKD.

SST IN THE PATHOPHYSIOLOGY OF ADPKD

ADPKD is predominantly caused by a mutation in the PKD1 gene, in 80% of cases, or in the PKD2 gene, in 10% of cases. In rare cases, other mutations are found, which have recently been identified [33, 34]. In the remainder of cases, the mutation that underlies the disease is not known. PKD1 encodes for the protein polycystin-1 and PKD2 for the protein polycystin-2 [35]. These proteins form the so-called polycystin complex that is localized at the base of the primary cilium, which acts as a mechanosensor detecting flow in the renal tubules. When this sensor is stimulated, calcium influx occurs from pre-urine into the cytoplasm of renal tubular epithelial cells and from intracellular stores. In ADPKD, the polycystin complex is dysfunctional and consequently calcium cannot enter the cells nor can calcium be released from intracellular stores. Low intracellular calcium leads to high activity of adenyl cyclase and reduced activity of calcium-sensitive cAMP-degrading enzyme (phosphodiesterase), which both lead to high intracellular cAMP levels. In turn, these high intracellular cAMP levels lead to aberrant renal tubular epithelial cell proliferation and chloride-driven fluid excretion in the kidney, the two key components of the process of cyst formation and growth in ADPKD [36] (Figure 2). In PLD, increased cholangiocyte proliferation and fluid secretion are the key features, which are stimulated by cholangiocyte cAMP [37].

As described, SST can lead via all its receptor subtypes to direct inhibition of adenyl cyclase and cAMP production. Furthermore, some SSTR subtypes can be coupled to various phospholipase C isoforms, leading to increased Ca2+ levels, which is an indirect mechanism by which SST can lead to lower intracellular cAMP (Figure 2). Therefore SST has the potential to slow disease progression in ADPKD. As described previously, endogenous SST reaches very low plasma concentrations, unable to trigger SST receptors. We have observed that SST concentrations are similar in ADPKD patients compared with healthy controls (A.L. Messchendorp et al., unpublished data). For this reason, SST needs to be administered to be of therapeutic use. However, administration of endogenous SST is of limited therapeutic potential since it is rapidly eliminated in vivo. Therefore analogues have been synthesized in which the biochemical stability of the peptide has been increased by incorporation of modified amino acids, which typically show selectivity for one or some of the SST receptor subtypes.

SST ANALOGUES

Based on differences in ring chemistry, size and position of bridging units, various analogues with different affinities for the SSTR subtypes exist. The most important and clinically used
**FIGURE 2**: Schematic representation of the pathophysiological processes that drive cyst formation and growth in renal tubular epithelial cells of the collecting duct in ADPKD and the mechanism of action of vasopressin V2 receptor antagonists and SST analogues. In ADPKD, the polycystin complex (formed by the proteins PC1 and PC2 on the apical membrane) is dysfunctional, which leads to diminished calcium influx or diminished release of calcium from intracellular stores. Low intracellular calcium levels in turn stimulate activation of adenylate cyclase (AC), which converts adenosine triphosphate into cAMP. cAMP is an important player in several pathways that could possibly lead to cyst expansion. cAMP increases cell proliferation via protein kinase A and activation of the Ras/Raf/ERK pathway. Furthermore, cAMP activates apical-positioned chloride channels (CFTR channels), leading to fluid secretion into the cyst lumen. cAMP production can be inhibited by blocking the vasopressin V2 receptor (V2R), which is coupled to G stimulatory (Gs) proteins that can activate AC. Activation of the SST receptor (SSTR) can inhibit cAMP production in a direct and indirect way. AC can be directly inhibited by the receptor-coupled G inhibitory (Gi) proteins. Activation of these Gi proteins can also activate calcium channels and stimulate intracellular release of calcium via phospholipase C, which can restore intracellular calcium stores. This leads indirectly to inhibition of cAMP production. Orange and grey lines indicate that the pathway is activated or inactivated, respectively.

**Table 1. SST analogues and their characteristics**

| SST analogue | Manufacturer | Receptor affinity | Registered indications | Administration route | Half-life | Dosing regimen |
|--------------|--------------|------------------|------------------------|----------------------|----------|----------------|
| Octreotide (SMS 201-995, Sandostatin) | Novartis Pharmaceuticals | SSTR2 > SSTR3, -5 | Acromegaly, Gastro-entero-pancreatic endocrine tumours, Advanced neuroendocrine tumours, TSH-secreting pituitary adenomas, Prevention of complications after pancreatic surgery, Acute oesophageal varical bleeding | IR, Subcutaneous | IR, Subcutaneous | IR, Subcutaneous 2–3× per day, Intravenous continuous LAR, 1× per 4 weeks |
| Lanreotide (BIM 23014, Somatuline) | Ipsen Ltd. | SSTR2 > SSTR3, -5 | Acromegaly, Gastro-entero-pancreatic-neuroendocrine tumours, Thyrotropic adenomas | ATG, Subcutaneous | ATG, 23–30 days | ATG, 1× per 4 weeks |
| Pasireotide (SOM-230, Signifor) | Novartis Pharmaceuticals | SSTR1, -2, -3, -5 | Acromegaly, Cushing’s disease | IR, Subcutaneous, LAR | IR, 12 h, 16 days | IR, 2× per day, LAR, 1× per 4 weeks |

IR, immediate-release; LAR, long-acting release; ATG, autogel; SR, slow-release. The information in this table is derived from https://www.medicines.org.uk/emc/. Year of last update 2016 for octreotide and lanreotide; 2017 for pasireotide; Year of access 2018.

SST analogues are octreotide, lanreotide and pasireotide. There is ample clinical experience with these drugs, as these drugs have been used for many years in neuroendocrine disorders like acromegaly to inhibit growth hormone secretion, but also to treat neuroendocrine tumours by inhibiting serotonin secretion. Different SST analogues, administration routes (intravenous, subcutaneous, intramuscular) and dosing regimens are used for the various indications (Table 1).
The most common adverse effects are summarized in Table 2. It is caused by receptor desensitization, as described earlier. This may or disappear after longer duration of the treatment. This may be caused by receptor desensitization, as described earlier. The most common adverse effects are summarized in Table 2.

| System         | Adverse effect                                                                 |
|----------------|--------------------------------------------------------------------------------|
| Gastrointestinal | Diarrhoea++, abdominal pain++, nausea++, constipation++, flatulence++, dyspepsia+, vomiting, abdominal bloating, steatorrhoea, loose stools++, discoloration of faeces++ |
| Hepatobiliary  | Cholelithiasis++, cholecystitis++, biliary sludge+, hyperbilirubinaemia+, acute pancreatitis |
| Glucoregulation | Hyperglycaemia++, diabetes mellitus++ |
| Cardiac        | Bradycardia++, tachycardia++, prolonged QT intervals++ |

**Adverse effects of SST analogues**

SST analogues, in general, elicit similar adverse effects, because they mostly interact with the same receptors. Most of the receptors are found in the gastrointestinal tract and consequently adverse effects are predominantly related to this tract. Pasireotide, however, seems to lead to hyperglycaemia and ECG abnormalities more often than the other SST analogues [39]. Interestingly, most of these adverse effects become milder or disappear after longer duration of the treatment. This may be caused by receptor desensitization, as described earlier. The most common adverse effects are summarized in Table 2.

Besides these adverse effects, there may also be ADPKD-specific adverse effects. In a recent randomized study [40], it became apparent that the use of SST analogues was associated with the development of hepatic cyst infection in patients with ADPKD. In the Developing Interventions to halt Progression of Autosomal dominant polycystic Kidney disease (DIPAK) 1 trial, which included patients with later-stage ADPKD, 9 hepatic cyst infection events in 8 subjects were noted in the 153 subjects that received lanreotide during 2.5 years of treatment and none in the 152 subjects of the control group. A literature review revealed that hepatic cyst infections also occurred in other studies with SST analogues in patients with ADPKD or PLD. Most of these complications were seen with lanreotide, but hepatic cyst infections have also been observed with other SST analogues [41]. The exact mechanism of hepatic cyst infections with SST analogues is unknown, but it has been suggested that a reduction in bile flow may play a role. Also, a history of hepatic cyst infections seems relevant. After a protocol amendment excluding patients with a history of hepatic cyst infections, the incidence of this complication decreased significantly in the aforementioned trial.

**STUDIES WITH SST ANALOGUES IN ADPKD**

Several preclinical and clinical studies have been conducted that studied the efficacy of SST analogues to inhibit cAMP production, hepatic and kidney cyst growth and renal function decline. It is remarkable that the first clinical study was performed before any preclinical data were available. The rationale for the first clinical study by Ruggenenti et al. [42] was based on an observation in a single ADPKD patient that received octreotide for acromegaly. In this specific patient, a potential beneficial effect of SST was considered because kidney function and kidney volume remained stable during treatment with octreotide. As there was extensive experience with SST analogues in the treatment of neuroendocrine disorders, a Phase III study with an SST analogue as treatment for ADPKD was started immediately, not awaiting pre-clinical data.

**Pre-clinical studies**

Only six experimental studies have been published that investigated the effects of SST analogues in experimental PKD. The results of these studies are summarized in Table 3 [43–48]. The first study, published in 2007 by Masyuk et al. [43], showed in an in vitro model of cystogenesis that octreotide inhibited cAMP levels by 35%. In vivo kidney and hepatic cyst growth, fibrosis and mitotic indices were reduced in the polycystic kidney (PCK) rat by 20–60%. After that landmark study, Spirli et al. [44] described in 2012 that the combination of octreotide and sorafenib (an inhibitor of tyrosine protein kinases and Raf kinases), but not octreotide alone, was effective in reducing the cystic area and proliferation in polycystin-2-defective mice. In 2013, Tietz Bogert et al. [45] developed a hepatic cyst model with zebrafish embryos. Hepatic cystogenesis was inhibited when these embryos were exposed to the SST analogue pasireotide. In the same year, Masyuk et al. [46] found that octreotide and pasireotide reduced intracellular CAMP levels and cell proliferation, affecting cell cycle distribution, decreasing the growth of cultured cysts in vitro and inhibiting hepatorenal cystogenesis in vivo in PCK rats and in PKD2(WS25/-) mice (a model for ADPKD). In that study, pasireotide in the applied dose was more potent than octreotide. In 2015, Hopp et al. [47] found in a hypomorphic PKD1 model that treatment with tolvaptan and pasireotide alone markedly reduced renal cyst progression and that the combination showed an additive effect. Furthermore, combination treatment significantly reduced cystic and fibrotic volume and decreased CAMP to wild-type levels. They also showed that hepatic hypertrophy could be corrected with pasireotide. Lastly, Kugita et al. [48] recently investigated the efficacy of treatment with pasireotide and octreotide in PCK rats. They showed that pasireotide and the combination of pasireotide with octreotide lowered kidney and liver weight, cystic volume and renal CAMP levels. Treatment with octreotide alone did not have an effect. In combination, these preclinical studies suggest that SST analogues can inhibit both renal and hepatic cystogenesis and therefore may inhibit ADPKD progression. These studies also point to possible differences in efficacy between SST analogues.

**Clinical studies**

At the moment, seven clinical studies have been completed with SST analogues in ADPKD patients. The results of these studies are summarized in Table 4 [42, 49–54]. These studies have uniformly shown that SST analogues can slow the growth in total liver volume. These studies also confirm the hypothesis that SST analogues have a beneficial effect on the renal cystic phenotype. Growth in total kidney volume (TKV) in subjects using SST analogues was less than in subjects using placebo in
most studies. However, results with respect to the rate of decline in kidney function are equivocal. From the seven clinical studies, there were a number that showed a beneficial effect on the rate of growth in total kidney and liver volume, but also a greater decline in estimated GFR (eGFR) with SST analogues than with placebo [42, 53]. However, these studies were all underpowered and of too short a duration to allow firm conclusions on the renoprotective effect of SST analogues. Later, the A Long-Acting somatostatin on Disease progression in Nephropathy due to autosomal dominant polycystic kidney disease (ALADIN) study was published, which included more subjects (n = 79) and was of longer duration (3 years) [52]. For the pre-specified efficacy outcomes [absolute change in TKV at Year 3 and slope of measured GFR (mGFR) from Years 0 to 3], no significant benefit of treatment with octreotide was observed [52]. That no beneficial effect of SST analogues was observed on the rate of kidney function decline in these studies may have several explanations. First, the effect of SST analogues on the rate of decline in kidney function is difficult to assess, because these drugs induce a biphasic effect on GFR. Shortly after the start of treatment, an alleged haemodynamic, reversible decrease in GFR is observed. Theoretically, a slower decline in the rate of annual GFR loss occurs thereafter that reflects the structural beneficial effect that is obtained with the SST analogue. Such a biphasic effect on eGFR has been observed with tolvaptan in ADPKD [6, 55] and with angiotensin-converting enzyme inhibitors in other renal diseases. As well, the clinical studies with SST analogues in ADPKD, which were of short duration in general, show a greater decline in eGFR with SST analogues than with placebo. When studying a drug with a biphasic effect on GFR, its chronic structural renoprotective effect should be investigated by studying the change in kidney function on

| References | SST analogue | Experimental design | Renal phenotype | Liver phenotype |
|------------|--------------|---------------------|----------------|----------------|
| Masyuk et al. [43] | Octreotide | In vitro: N = 15 PCK bile ducts grown in 3-dimensional culture with Oct or vehicle | In vitro: NA | In vitro: 35% reduction in cAMP levels |
| | | In vivo: N = 60 PCK rats treated with Oct or vehicle 4–16 weeks | In vivo: 19–39% reduction in kidney weight, renal cystic volume and renal fibrosis | 44% reduction in cyst growth |
| Spirli et al. [44] | Octreotide and sorafenib | In vivo: N = 32 Pkd2cKO mice treated with vehicle, sorafenib, Oct or sorafenib/Oct 8 weeks | In vivo: NA | In vivo: Reduction in liver cyst volume, proliferation (Ki67), liver weight and increased apoptosis (CC3) |
| Tietz Bogert et al. [45] | Pasireotide | In vivo: N = 800 Zebrafish injected with morpholinos sec63, prkcsb and pkd1a (PLD model) or control buffer and treated with pasireotide, VK3 or 4-PBA | In vivo: NA | In vivo: Reduction of hepatic cystogenesis |
| Masyuk et al. [46] | Octreotide and pasireotide | In vitro: Cholangiocytes from control and PCK rats, healthy humans and ADPKD patients, normally cultured or in Oct or pasireotide | In vitro: NA | In vitro: Reduction of CAMP levels, cell proliferation (Oct 9.6–18.4%/pasireotide 18.6–33.7%) and hepatic cyst expansion (Oct 1.6–2.3%/pasireotide 2.2–4.7x) |
| | | In vivo: N = 27 PCK rats and N = 14 Pkd2wox25/ mice treated with Oct, pasireotide or vehicle 6 weeks | In vivo: Reduction of kidney weight (Oct 16%/pasireotide 20%), cystic volume (Oct 19%/pasireotide 30%), fibrotic volume (Oct 18%/pasireotide 25%) | In vivo: Reduction of liver weight (Oct 9%/pasireotide 16%), cystic areas (Oct 24%/pasireotide 36%), fibrotic areas (Oct 10%/pasireotide 19%) |
| Hopp et al. [47] | Pasireotide (and tolvaptan) | In vivo: N = 81 Pkd1(RC/RC) mice receiving no treatment, tolvaptan, pasireotide or tolvaptan/pasireotide 5 months | In vivo: Reduction in kidney weight, cystic volume, fibrotic volume and CAMP level with tolvaptan/pasireotide >tolvaptan or pasireotide | In vivo: Reduction of hepatocyte hypertrophy by pasireotide |
| Kugita et al. [48] | Octreotide and pasireotide | In vivo: N = 24 PCK rats treated with vehicle, Oct, pasireotide or Oct/pasireotide 12 weeks | In vivo: Reduction of kidney weight, cystic volume, proliferation (Ki67) and CAMP levels in pasireotide or Oct/pasireotide | In vivo: NA |

Oct, octreotide; NA, not applicable.

Somatostatin in ADPKD 1311
Table 4. Summary of studies performed with SST analogues in ADPKD

| References                  | SST analogue | Trial design | Effect versus control on GFR = kidney function | TKV | TLY |
|-----------------------------|--------------|--------------|-------------------------------------------------|-----|-----|
| Ruggenenti et al. [42]      | Octreotide   | N = 14 ADPKD Cross-over 6 months | Not significant Pla: −0.2 versus Oct: −5.5 mL/min/1.73 m² NS | Significant benefit Pla: +6.6 versus Oct: +3.6% P < 0.05 | Significant benefit Pla: +1.2 versus Oct: −4.4% P < 0.05 |
| van Keimpema et al., 2009 [49] | Lanreotide  | N = 54 PLD/ADPKD RCT 6 months | Not stated Benefit Pla: +3.5 versus Lan: −1.5% P = 0.08 | Significant benefit Pla: +1.6 versus Lan: −2.9% P < 0.01 |
| Chrispijn et al., 2012 [50] | Lanreotide   | N = 41 PLD/ADPKD Open label FU of Keimpema, 2009 Not stated 12 months | No control group Benefit Lan: −1% NS | No control group Benefit Lan: −4% P < 0.05 |
| Hogan et al., 2012 [51]     | Octreotide   | N = 42 PLD/ADPKD RCT 12 months | Not significant Pla: −7.2 versus Oct: −5.1% NS | Significant benefit Pla: +8.61 versus Oct: +0.25% P < 0.05 | Significant benefit Pla: +0.92 versus Oct: −4.95% P < 0.05 |
| Caroli et al. [52]          | Octreotide   | N = 79 ADPKD RCT 3 years | Primary analysis (slope Years 0–3) Pla: −4.95 versus Oct: −3.85 mL/min/1.73 m²/year NS | Primary analysis (absolute change at Year 3) Significant benefit Pla: +454 versus Oct: −220 mL P = 0.25 Post hoc analysis (slope Years 1–3) Significant benefit Pla: −4.32 versus Oct: −2.28 mL/min/1.73 m²/year P < 0.05 | No control group Benefit Lan: −1% Pla: +152 versus Oct: +77 mL/year P < 0.05 |
| Gevers et al. [53]          | Lanreotide   | N = 43 ADPKD Uncontrolled 6 months | No control group Lan: −3.5% P < 0.001 | No control group Lan: −1.7% P < 0.001 | No control group Lan: −3.1% P < 0.001 |
| Meijer et al., 2018 [54]    | Lanreotide   | N = 305 ADPKD Open-label RCT 2.5 years | Not significant Benefit Co: −3.46 versus Lan: −3.53 mL/min/1.73 m²/year NS | Significant benefit Co: 5.56 versus Lan: 4.15% P = 0.02 | Overall Co: 2.9 vs. Lan: −0.9%, P = 0.001 Subgroup with liver volume > 2L Co: 3.92 vs. Lan: −1.99%, P < 0.001 |

Pla, placebo; Oct, octreotide; Lan, lanreotide; co, control; NS, not significant TLV, total liver volume.
A larger, open-label randomized controlled trial (RCT) was performed by our study group, investigating the effects of 2.5 years of treatment with the SST analogue lanreotide in 305 ADPKD patients with an eGFR or 30–60 mL/min/1.73 m² the DIPAK 1 study [54]. Given the aforementioned experience, change in kidney function on treatment was chosen as the primary outcome. This study confirmed that lanreotide significantly reduced liver and kidney cyst growth. However, no attenuation of eGFR slope was observed. The rate of eGFR loss on treatment, the primary endpoint of the study, was −3.53 with lanreotide versus −3.46 mL/min/1.73 m²/year in the control group. The difference between both groups was only −0.08 [confidence interval (95% CI) −0.71–0.56] mL/min/1.73 m²/year and not significant (P = 0.81). When the secondary endpoint, annual rate of eGFR loss, was calculated using only the pre- versus post-treatment eGFR values, no effect of lanreotide was observed (Figure 3, left panel). A prespecified subgroup analysis did not provide evidence that lanreotide improved the primary outcome in any of the subgroups studied. For TKV, however, the results were beneficial. The rate of change in height adjusted TKV (hTKV) between the pre- and post-treatment visit was significantly lower in the lanreotide group: 4.15%/year (95% CI 3.33–4.99) versus 5.56 (95% CI 4.76–6.36) in the control group [difference −1.33%/year (95% CI −2.41 to −0.24), P = 0.02], corresponding with a 24% reduction in hTKV growth rate (Figure 3, right panel). The benefit of lanreotide on hTKV growth was observed in all subgroups tested. The change in hTKV was also assessed using data from the magnetic resonance imaging (MRI) at the end of the treatment period instead of the MRI at the post-treatment visit. In that case, the difference between both groups in the hTKV growth rate was stronger [−2.14%/year (95% CI −3.14 to −1.12, P < 0.001), indicating that after stopping lanreotide treatment, some rebound occurs, but a beneficial effect on kidney volume is maintained even after stopping treatment. Currently there is one clinical study ongoing with SST analogues in ADPKD patients and two studies that are finalized but not yet published (Table 5) [56–58].

**IS THERE A PLACE FOR SST ANALOGUES IN ADPKD?**

The DIPAK 1 study provides convincing evidence that lanreotide does not slow the rate of renal function decline in later-stage ADPKD. Can we, therefore, state that there is no role for SST analogues in the treatment of the renal phenotype of ADPKD? This may not necessarily be true since lanreotide did show an effect on growth in TKV and liver volume. This is surprising because it is a paradigm in nephrology that effects on TKV can be used as a surrogate marker for effects on kidney function. The question arises whether the divergent treatment effects on GFR and TKV are explained by trial design or are they drug specific?

In this respect, an important difference in trial design between the DIPAK 1 and ALADIN studies was that the ALADIN study had mGFR as the outcome (plasma clearance of the exogenous filtration marker iohexol), whereas the DIPAK 1 study used GFR estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine formula. As is generally known, creatinine is not only filtrated by the glomerulus, but also partially secreted by renal tubular cells. This is accounted for in the CKD-EPI formula [59]. Because ADPKD is a disease characterized by an increase in renal tubular cell...
mass, it may be that the GFR estimation equations perform less well in patients with this disease. Indeed, one study concluded that in ADPKD, equations used to estimate GFR may be less reliable and may fail to detect changes in GFR over time [60]. Two other reports, however, showed that equations to estimate GFR perform as well in ADPKD as in non-ADPKD CKD patients [61, 62]. More importantly, when alternative measures of GFR were used, such as GFR estimated with plasma cystatin C, 24-h urinary creatinine clearance or serum urea, similar results were obtained. These latter data indicate that the results of the DIPAK 1 study are robust.

A second option related to trial design of the DIPAK 1 study, which may explain why lanreotide did not preserve kidney function, could be that patients were studied with later-stage ADPKD. It could be that in later-stage ADPKD, SST receptors are expressed less because of fibrosis formation, as has been shown for the vasopressin V2 receptor in animal experiments, [63] or that patients reached a point of ‘no return’ beyond which other disease processes have become important and cannot be improved by an SST analogue [64]. However, subgroup analysis of the DIPAK 1 study showed no differences in treatment effect between CKD Stages 3a and 3b, but in earlier disease the situation may be different.

The third option related to trial design could be that the dosage of lanreotide was suboptimal in the DIPAK 1 study. This is less likely because a dosage of lanreotide was used that has been shown to be effective in neuroendocrine disorders. However, it may be that the expression of SSTRs in the kidney is too low for SST analogues to be effective. As far as known, only one study, performed by our study group, has investigated SSTR expression specifically in ADPKD. We observed in two conditional Pkd1 models that SSTR2 expression levels are reduced during kidney cyst growth. In addition, we saw a significant decrease in SSTR2 expression in epithelia of dilated tubules and cystic epithelia in mice with end-stage PKD compared with wild-type mice. Data of human biopsies, however, are ambiguous [25]. Importantly, in the DIPAK 1 study, there was a beneficial effect of lanreotide on TKV growth. This suggests that SSTRs are expressed in the human ADPKD kidney.

The question then emerges whether the results of the DIPAK 1 study are specific for lanreotide or class related? Octreotide, for example, investigated in the ALADIN study, has slightly more affinity for SSTR2 and SSTR3 and slightly less affinity for SSTR5 as compared with lanreotide [39]. Whether this results in a difference in clinical efficacy in ADPKD is doubtful, because octreotide has been shown to be equally effective in the treatment of acromegaly compared with lanreotide, and both drugs elicit similar adverse effects [65]. Pasireotide, on the other hand, has more marked differences in receptor affinity compared with lanreotide, which more likely could result in a different treatment effect in ADPKD [66]. Also, pasireotide has been shown to be effective in the treatment of Cushing’s disease in contrast to octreotide [67], to be more effective in the treatment of acromegaly compared with octreotide [68] and to be more effective than octreotide in two experimental models for ADPKD [46, 48]. More severe hyperglycaemic side effects and frequent ECG abnormalities [39], however, are expected to limit the widespread clinical use of pasireotide for ADPKD, a disease for which lifelong treatment is needed.

Taking the above discussion into account, it may also be argued that treatment effects on GFR and TKV are unrelated (see also Figure 3). That is remarkable, because it is a paradigm that in ADPKD, TKV is related to GFR and can be used as a surrogate outcome, especially in trials in early stages of the disease. However, it could also be that lanreotide has an intrinsic nephrotoxic effect that offsets any potential benefit that could be obtained via its effect on hTKV. However, such a nephrotoxic effect is not known from the literature in non-ADPKD patients. Other potential explanations could be that the effect on TKV growth was not large enough to translate into a functional benefit in the duration of the clinical trial, that it takes more time before a benefit on TKV translates into a benefit on the rate of GFR loss or that patients were included with later-stage ADPKD, in whom growth in TKV may have a less dominant role in causing eGFR loss than in earlier-stage disease.

For now, we may conclude that there is no role for SST analogues to preserve kidney function in ADPKD, unless future data prove differently. However, the available evidence shows that SST analogues do have a beneficial effect on the growth of TKV and liver volume. ADPKD patients with a high intra-abdominal volume and related symptoms may therefore be the target group for treatment with these agents, to prevent or postpone the need for liver transplantation. Because of the possible higher incidence of hepatic cyst infections with SST analogues, it seems wise to exclude patients with a history of hepatic cyst infection from such treatment.

### Table 5. Summary of ongoing or finalized but as yet unpublished studies with SST analogues in ADPKD [56–58]

| Institute                      | SST analogue | Trial design | Inclusion criteria | Clinical endpoint | ClinicalTrials.gov identifier |
|--------------------------------|--------------|-------------|--------------------|------------------|-------------------------------|
| Mayo Clinic, Rochester, MN, USA | Pasireotide  | RCT         | PLD >4000 mL       | Change in TLV     | NCT 01670110                  |
|                               | 60 mg s.c., 1×28 days | 12 months               | Age >18 years eGFR >30 mL/min/1.73 m² | Change in mGFR | NCT 01377246                  |
| Mario Negri Institute, Milan, Italy | Octreotide    | RCT/28 days | N = 100            | Change in mGFR    | Change in TKV                  |
|                               | 40 mg s.c., 1×28 days | 36 months               | Age >18 years eGFR 15–40 mL/min/1.73 m² | Change in mGFR | NCT02127437                   |
| Necker Hospital, Paris, France | Lanreotide   | RCT         | N = 180            | Change in mGFR    |                               |
|                               | 120 mg s.c., 1×28 days | 36 months               | Age >18 years eGFR 30–89 mL/min/1.73 m² |                               |                               |

s.c., subcutaneous.
Among the pivotal detrimental factors in the pathophysiology of ADPKD are elevated cAMP levels. Although therapies to slow the rate of disease progression in ADPKD have emerged, there is still an important unmet need for new therapies. In this review, we show that SST analogues are theoretically promising as therapeutic agents since these drugs inhibit cAMP production. Both preclinical and preliminary clinical studies suggest beneficial effects of SST analogues in the treatment of ADPKD. However, a recent large-scale RCT showed no beneficial effect of lanreotide on the rate of kidney function decline in patients with later-stage ADPKD despite a beneficial effect on kidney growth. Results of ongoing trials should be awaited before definitive conclusions can be drawn with respect to renoprotection, because results may be different with other SST analogues or in patients with earlier-stage disease. For now, treatment of ADPKD patients with these agents should be limited to patients with a high intra-abdominal volume and related symptoms.

**REFERENCES**

1. Neumann HP, Jilg C, Bacher J et al. Epidemiology of autosomal-dominant polycystic kidney disease: an in-depth clinical study for south-western Germany. Nephrol Dial Transplant 2013; 28: 1472–1487
2. Bae KT, Zhu F, Chapman AB et al. Magnetic resonance imaging evaluation of hepatic cysts in early autosomal-dominant polycystic kidney disease: the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease cohort. Clin J Am Soc Nephrol 2005; 1: 64–69
3. Abu-Wasel B, Walsh C, Keough V et al. Pathophysiology, epidemiology, classification and treatment options for polycystic liver diseases. World J Gastroenterol 2013; 19: 5775–5786
4. van Keimpema L, Nevens F, Adam R et al. Excellent survival after liver transplantation for isolated polycystic liver disease: an European Liver Transplant Registry study. Transpl Int 2011; 24: 1239–1245
5. Chebib FT, Sussman CR, Wang X et al. Vasopresxin and disruption of calcium signalling in polycystic kidney disease. Nat Rev Nephrol 2015; 11: 451–464
6. Torres VE, Chapman AB, Devuyst O et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367: 2407–2418
7. Torres VE, Chapman AB, Devuyst O et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med 2017; 377: 1930–1942
8. Mancinelli R, Franchitto A, Glaser S et al. Vasopresxin regulates the growth of the biliary epithelium in polycystic liver disease. Lab Invest 2016; 96: 1147–1155
9. Gevers TJ, Drenth JP. Diagnosis and management of polycystic liver disease. Nat Rev Gastroenterol Hepatol 2013; 10: 101–108
10. Krulich L, Dharwad AP, McCann SM. Stimulatory and inhibitory effects of purified hypothalamic extracts on growth hormone release from rat pituitary in vitro. Endocrinology 1968; 83: 783–790
11. Hellman B, Lemmark A. Evidence for an inhibitor of insulin release in the pancreatic islets. Diabetologia 1969; 5: 22–24
12. Brazau P, Vale W, Burgus R et al. Hypothalamic polypeptide that inhibits the secretion of immuno-reactive pituitary growth hormone. Science 1973; 179: 77–79
13. Patel YC, Liu JL, Galanopoulou AS et al. Production, action, and degradation of somatostatin. In: LS Jefferson, AD Cherrington, HM Goodman (eds). The Handbook of Physiology, the Endocrine Pancreas and Regulation of Metabolism. New York: Oxford University Press, 1999: 267–302
14. Zabel BU, Naylor SL, Sakaguchi AY et al. High-resolution chromosomal localization of human genes for amylase, proopiomelanocortin, somatostatin, and a DNA fragment (D3S1) by in situ hybridization. Proc Natl Acad Sci USA 1983; 80: 6932–6936
15. Patel YC. Somatostatin and its receptor family. Front Neuroendocrinol 1999; 20: 157–198
16. Patel YC, Wheatley T, Ning C. Multiple forms of immuno-reactive somatostatin: comparison of distribution in neural and nonneural tissues and portal plasma of the rat. Endocrinology 1981; 109: 1943–1949
17. Ensink JW, Laschansky EC, Vogel RE et al. Circulating prosomatostatin-derived peptides. Differential responses to food ingestion. J Clin Invest 1989; 83: 1580–1589
18. Shoelson SE, Polonsky KS, Nakabayashi T et al. Circulating forms of somatostatin like immuno-reactivity in human plasma. Am J Physiol 1986; 250: E428–E434
19. Hoeldtke RJ, Lamberts SW. The pathophysiological consequences of somatostatin receptor internalization and resistance. Endoc Rev 2003; 24: 28–47
20. Turman MA, O’Dorisio MS, O’Dorisio TM et al. Somatostatin expression in human renal cortex and mesangial cells. Regul Pept 1997; 68: 15–21
21. Turman MA, Apple CA. Human proximal tubular epithelial cells express somatostatin: regulation by growth factors and cAMP. Am J Physiol 1998; 274: F1095–F1101
22. Bhadari S, Watson N, Long E et al. Expression of somatostatin and somatostatin receptor subtypes 1-5 in human normal and diseased kidney. J Histochem Cytochem 2008; 56: 733–743
23. Balča DA, O’Dorisio MS, Summers MA et al. Segmental expression of somatostatin receptor subtypes sst5 and sst1 in tubules and glomeruli of human kidney. Am J Physiol Renal Physiol 2001; 280: F457–F465
24. Unger N, Ueberberg B, Schulz S et al. Somatostatin: regulation by growth factors and cAMP. Exp Clin Endocrinol Diabetes 2012; 120: 482–489
25. Lin C, Happe H, Verarr K et al. The expression of somatostatin receptor 2 decreases during cyst growth in mice with polycystic kidney disease. Exp Biol Med (Maywood) 2018; 243: 1092–1098
26. Jones CR, Millar JA, Lawrie C et al. Specific inhibition of aldosterone responses to endogenous and exogenous angiotensin II by somatostatin. Clin Endocrinol (Oxf) 1984; 21: 279–284
27. Sieber C, Gnaiger M, Del Pozo E et al. Effect of a new somatostatin analogue SMS 201-955 (Sandostatin) on the renin-aldosterone axis. Clin Endocrinol (Oxf) 1988; 28: 25–32
28. Ray C, Carney S, Morgan T et al. Somatostatin as a modulator of distal nephron water permeability. Clin Sci 1993; 84: 455–460
29. Hatzoglou A, Bakogeorgou E, Papakonstanti E et al. Identification and characterization of opioid and somatostatin binding sites in the opossum kidney (OK) cell line and their effect on growth. J Cell Biochem 1996; 63: 410–421
30. Schmidt A, Pleiner J, Schaller G et al. Renal hemodynamic effects of somatostatin are not related to inhibition of endogenous insulin release. Kidney Int 2002; 61: 1788–1793
31. Winkler SN, Torikai S, Levine BS et al. Effect of somatostatin on vasopressin-induced anti-diuresis and renal cyclic AMP of rats. Miner Electrolyte Metab 1982; 7: 8–14
32. Ishikawa S, Saito T, Kuzuya T. Reversal of somatostatin inhibition of AVP-induced cAMP by pertussis toxin. Kidney Int 1988; 33: 536–542
33. Porath B, Gainullin VG, Corne-Le Gall E et al. Mutations in GANAB, encoding the glucosidase IIX subunit, cause autosomal-dominant polycystic kidney and liver disease. Am J Hum Genet 2016; 98: 1193–1207
34. Corne-Le Gall E, Olson RJ, Besse W et al. Monoallelic mutations to GANAB11 cause atypical autosomal-dominant polycystic kidney disease. Am J Hum Genet 2018; 102: 832–844
35. Grantham JJ, Torres VE, Chapman AB et al. Volume progression of polycystic kidney disease. N Engl J Med 2006; 354: 2122–2130
36. Torres VE, Harris PC. Strategies targeting CAMP signaling in the treatment of polycystic kidney disease. J Am Soc Nephrol 2014; 25: 18–32
41. Lantinga MA, D'Agnolo HMA, Casteleijn NF et al
42. Ruggenenti P, Remuzzi A, Ondei P et al
43. Masyuk TV, Masyuk AI, Torres VE et al
44. Spirli C, Morell CM, Locatelli L et al
45. Tietz Bogert PS, Huang BQ, Gradilone SA et al
46. Hogan MC, Masyuk TV, Page L et al
47. Alvaro D, Giglioazzi A, Attiì AF. Regulation and deregulation of cholangiocyte proliferation. J Hepatol 2000; 33: 333–340
48. Weckbecker G, Lewis I, Albert R et al. Opportunities in somatostatin research: biological, chemical and therapeutic aspects. Nat Rev Drug Discov 2003; 2: 999–1017
49. Giustina A, Mazziotti G, Maffezzoni F et al. Investigational drugs targeting somatostatin receptors for treatment of acromegaly and neuroendocrine tumors. Expert Opin Invest Drugs 2014; 23: 1619–1635
50. Meijer E, Drenth JPH, d'Agnolo H et al. Rationale and design of the DIPAK 1 study: a randomized controlled clinical trial assessing the efficacy of lanreotide to halt disease progression in autosomal dominant polycystic kidney disease. Am J Kidney Dis 2014; 63: 446–455
51. Lantinga MA, D'Agnolo HMA, Casteleijn NF et al. Hepatic cyst infection during use of the somatostatin analog lanreotide in autosomal dominant polycystic kidney disease: an interim analysis of the randomized open-label multicenter DIPAK-1 study. Drug Saf 2017; 40: 153–167
52. Ruggenenti P, Remuzzi A, Ondei P et al. Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. Kidney Int 2005; 68: 206–216
53. Masyuk TV, Masyuk AI, Torres VE et al. Octreotide inhibits hepatic cystogenesis in a rodent model of polycystic liver disease by reducing cholangiocyte adenosine 3', 5'-cyclic monophosphate. Gastroenterology 2007; 132: 1104–1116
54. Spirili C, Morell CM, Locatelli L et al. Cyclic AMP/PKA-dependent paradoxical activation of Raf/MEK/ERK signaling in polycystin-2 defective mice treated with sorafenib. Hepatology 2012; 56: 2363–2374
55. Tietz Bogert PS, Huang BQ, Gradilone SA et al. The zebrafish as a model to study polycystic liver disease. Zebrafish 2013; 10: 211–217
56. Masyuk TV, Radtke BN, Stroope AJ et al. Pasireotide is more effective than octreotide in reducing hepatorenal cystogenesis in rodents with polycystic kidney and liver diseases. Hepatology 2013; 58: 409–421
57. Hopp K, Hommerding CJ, Wang X et al. Tolvaptan plus pasireotide shows enhanced efficacy in a PKD1 model. J Am Soc Nephrol 2015; 26: 39–47
58. Kugita M, Nishii K, Yamaguchi T et al. Beneficial effect of combined treatment with octreotide and pasireotide in PKC rats, an orthogonal model of human autosomal recessive polycystic kidney disease. PLoS One 2017; 12: e0177934
59. van Keimpema L, Nevens F, Vanslambrouck R et al. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2009; 137: 16618.e1–2
60. Chrispijn M, Nevens F, Gevers TJ et al. The long-term outcome of patients with polycystic liver disease treated with lanreotide. Aliment Pharmacol Ther 2012; 35: 266–274
61. Hogan MC, Masyuk TV, Page L et al. Somatostatin analog therapy for severe polycystic liver disease: results after 2 years. Nephrol Dial Transplant 2012; 27: 3532–3539
62. Caroli A, Perico N, Perna A et al. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. Lancet 2013; 382: 1485–1495
63. Meijer E, Visser FW, van Aerts RMM et al. Effect of Lanreotide on Kidney Function in Patients With Autosomal Dominant Polycystic Kidney Disease: The DIPAK 1 Randomized Clinical Trial. JAMA 2018; 320: 2010–2019
64. Boerrien WE, Meijer E, de Jong PE et al. Short-term effects of tolvaptan in individuals with autosomal dominant polycystic kidney disease at various levels of kidney function. Am J Kidney Dis 2015; 65: 833–841
65. Hogan M. Pasireotide LAR in Severe Polycystic Liver Disease (SOM230). www.clinicaltrials.gov; NCT 01670110. 2017; 2018
66. Hogan M. Pasireotide LAR in Severe Polycystic Kidney Disease. www.clinicaltrials.gov; NCT01577246. 2018; 2018
67. Assistance Publique - Hôpitaux de Paris. Lanreotide In Polycystic Kidney Disease Study (LIPS). www.clinicaltrials.gov; NCT02127437. 2017; 2018
68. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612
69. Ruggenenti P, Gaspari F, Cannata A et al. Measuring and estimating GFR and treatment effect in ADPKD patients: results and implications of a longitudinal cohort study. PLoS One 2012; 7: e32533
70. Orskov B, Borresen ML, Feldt-Rasmussen B et al. Estimating glomerular filtration rate using the new CKD-EPI equation and other equations in patients with autosomal dominant polycystic kidney disease. Am J Nephrol 2010; 31: 53–57
71. Spithoven EM, Meijer E, Boerrien WE et al. Tubular secretion of creatinine in autosomal dominant polycystic kidney disease: consequences for cross-sectional and longitudinal performance of kidney function estimating equations. Am J Kidney Dis 2013; 62: 531–540
72. Meijer E, Gangsevoort RT, de Jong PE et al. Therapeutic potential of vasopressin V2 receptor antagonist in a mouse model for autosomal dominant polycystic kidney disease: optimal timing and dosing of the drug. Nephrol Dial Transplant 2011; 26: 2445–2453
73. Grantham JI, Torres VE. The importance of total kidney volume in evaluating progression of polycystic kidney disease. Nat Rev Nephrol 2012; 8: 667–677
74. Auriemma RS, Pivonello R, Gallardo M et al. Octreotide-LAR vs lanreotide-SR as first-line therapy for acromegaly: a retrospective, comparative, head-to-head study. J Endocrinol Invest 2008; 31: 956–965
75. Cuevas-Ramos D, Fleseriu M. Pasireotide: a novel treatment for patients with acromegaly. Drug Des Devel Ther 2016; 10: 227–239
76. Pivonello R, Petersenn S, Newell-Price J et al. Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing’s disease: results from a Phase III study. Clin Endocrinol 2014; 81: 408–417
77. Colao A, Bronstein MD, Freda P et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab 2014; 99: 791–799

Received: 24.10.2018; Editorial decision: 15.2.2019