Evidence-based treatment with somatostatin analogues in polycystic liver disease

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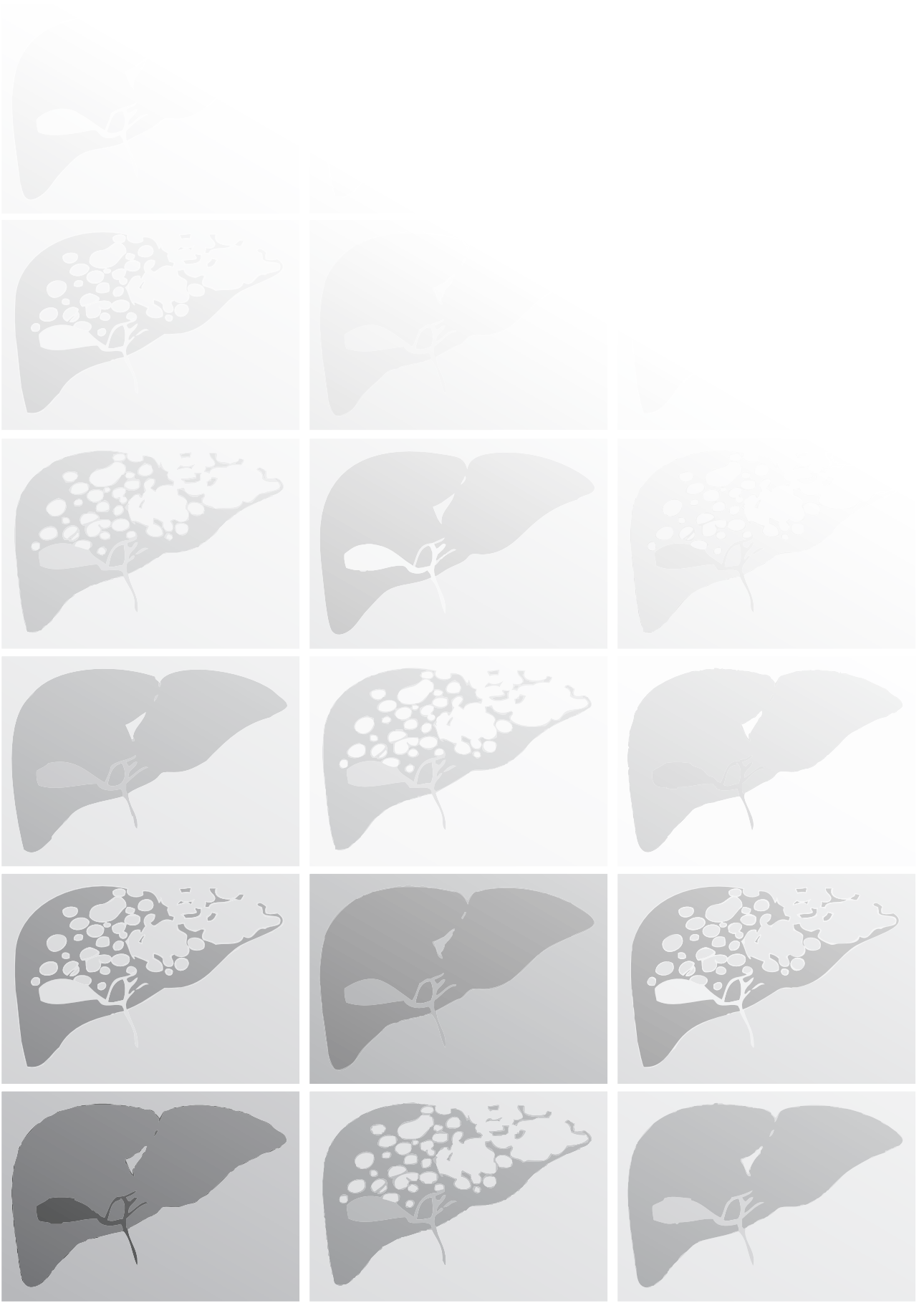
Outline Chapters Thesis



Chapter 1

General Introduction

Partly based on: Diagnosis and management of polycystic liver disease. Gevers TJG, Drenth JPH. Nat Rev Gastro Hepat. 2013; Feb;10(2):101-8

Introduction

Polycystic liver disease (PLD) is a rare condition characterized by the formation of numerous liver cysts.[1] It can be present in the combination with renal cysts as a manifestation of autosomal dominant polycystic kidney disease (ADPKD), or isolated as autosomal dominant polycystic liver disease (PCLD; Box 1).[8] For a long time PCLD and ADPKD were assumed to be phenotypic variants, although they now are regarded as genetically distinct. As both disorders have polycystic livers in common, they probably share pathophysiologic pathways.

Box 1. Underlying genetic diseases in PLD

PCLD

PCLD is rare, with an approximate prevalence of 1:158,000 based on a Dutch cohort study.[1] It is caused by *PRKCSH* or *SEC63* mutations, although in only ~20% of patients a bonafide mutation can be found.[2] These genes encode the proteins hepatocystin and SEC63, both involved in folding and quality control of glycoproteins in the endoplasmatic reticulum.[3-5] The *LRP5* mutation was recently discovered as a new causative gene in PCLD.[6]

ADPKD

ADPKD is the most common genetic cause of end-stage renal disease, with a worldwide prevalence of 0.1-0.2%.[7] ADPKD is inherited in an autosomal dominant fashion, and so far two genes, *PKD1* and *PKD2*, have been implicated to cause the disease in almost 100% of cases.[9] These genes encode two transmembrane proteins, polycystin-1 and polycystin-2, which are located at the primary cilium of cells.[11]

Ductal plate malformation

PLD probably results from ductal plate malformation during fetal development.[10] The ductal plate is the anatomical template for the development of the intrahepatic bile ducts.[12] A lack of adequate remodeling of the ductal plate during morphogenesis of the bile duct leads to persistence of embryonic biliary structures that consist of elongated lumina and do not communicate with normal ducts (Figure 1). It is thought that ductal

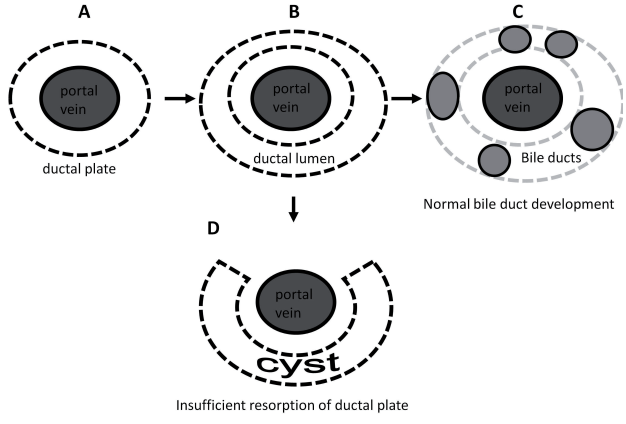


Figure 1: Embryonic development of the ductal plate. A. During early embryogenesis, a single-layer ductal plate surrounds the portal vein. B. Double-layered plates are then formed. C. Resorption of the ductal plate leads to the formation of a network of bile ducts. D. Insufficient resorption of the ductal plate leads to large dilated segments of the primitive bile duct and is considered to be the cause of cyst formation.

plate malformations represent the pathological basis of fibro(poly)cystic liver disorders such as biliary micro-hamartomas, Caroli's syndrome, autosomal recessive polycystic kidney disease, PCLD and ADPKD.[13, 14]

Hepatic cystogenesis

Experimental studies have provided evidence for the presence of cholangiocyte hyperproliferation and enhanced fluid secretion in cyst expansion.[15] These mechanisms are initiated by several signal transduction pathways that are aberrantly activated in polycystic livers. First, estrogens and vascular endothelial growth factors are overexpressed in hepatic cystic epithelium and promote proliferation of cholangiocytes through autocrine and paracrine mechanisms.[16, 17] Second, hepatic cysts exhibit markedly higher levels of phosphor-mammalian target of rapamycin (mTOR), which suggests that the mTOR pathway might modulate growth of liver cysts.[18] Third, mTOR controls the major transcriptional factor for VEGF (hypoxia-inducible factor-1α) and seems to be essential for its proliferative, antiapoptopic and proangiogenic effects.[17] Finally, cysts have high levels of adenosine 3',5' – cyclic monophospate (cAMP), which contributes to cholangiocyte proliferation and fluid secretion by activating several cAMP mediators, such as protein kinase A.[19-21] The elucidation of these pathways involved in hepatic cystogenesis led to the development of novel therapeutic approaches in PLD.

Natural course

Hepatic cysts are always present in PCLD, and are highly prevalent in ADPKD (67%-83%).[22] Although genetic and phenotypic differences exist between PCLD and ADPKD, the natural history of PLD is to a large extent similar for both disorders.[8] The clinical course of PLD dictates a continuous progression of size and number of hepatic cysts and is usually diagnosed during the fourth or fifth decade of life. The rate of progression is not known at this time but data from the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) sheds some insight in the natural history of liver cysts in ADPKD. Their study shows that the mean growth of a single liver cyst is about 1,13 ml in one year.[22] Three recent trials with octreotide and lanreotide in patients with PLD showed an annual growth of liver volume of 0.9-3.2%.[23-25] PLD tends to be more severe in females as they acquire cysts earlier in life and develop more cysts during their lifetime.[26] Other risk factors for hepatic cyst growth are age, renal cyst volume, severity of renal disease, prior pregnancies, and estrogen use.[1, 27-29] Indeed, 1 year of estrogen use in postmenopausal ADPKD patients selectively increases total liver volume by 7%, whereas total kidney volume remains unaffected.[30]

Diagnostic criteria

Currently, we lack unified diagnostic criteria for PLD. Abnormalities in liver enzyme levels are generally absent, with the exception of γ-glutamyltransferase and alkaline phosphatase in severe PLD, and are thus not useful in the diagnostic process.[8] At present, the diagnosis of PLD is made by imaging and is arbitrarily defined by the presence of more than 20 liver cysts as measured by ultrasound, CT or MRI.[1] Both underlying disorders of PLD (ADPKD and PCLD) have their own radiological diagnostic criteria. While ADPKD is diagnosed using the adjusted Ravine criteria, a PCLD diagnosis is made when a polycystic liver is present and no fulfilment of aforementioned ADPKD criteria.[31] However, in families with

isolated PLD, ≥ 4 liver cysts can be sufficient for a PCLD diagnosis.[32] Clinical differentiation between PCLD and ADPKD as the underlying disease remains difficult in patients without a positive family history, as PCLD patients may have a few renal cysts and ADPKD patients may possess polycystic livers as a predominant feature. Although mutation analysis is rarely performed in routine clinical practice, it can be helpful in these cases.

Disease severity

The severity and distribution of cysts in PLD can be classified according to the Gigot criteria, which categorizes according to number and size of liver cysts and the amount of remaining liver parenchyma (Figure 2).[33] Patients with <10 large (>10 cm) cysts are classified as type I. Type II include patients with diffuse involvement of liver parenchyma by multiple medium-sized cysts with remaining large areas of noncystic liver parenchyma. In type III massive diffuse involvement of liver parenchyma by small- and medium-sized liver cysts and only a few areas of normal liver parenchyma are present.[33] Gigot type I livers technically do not classify as a polycystic liver, due to the low number of liver cysts. Although the Gigot criteria are useful for crude determination of severity of PLD, the extent of the disease is at present more accurately assessed by CT or MRI volumetry.[24, 34, 35] A commonly used CT/MRI volumetry method is segmentation, which is the manual delineation of transversal CT or MRI images and subsequent interpolation by imaging software. Other methods for estimating volumes are stereology-based approaches.[24, 36] Although manual volumetry is very time-consuming (60-90 minutes), it is at present the most accurate method to determine liver size, with excellent intra- and interobserver variability.[23]

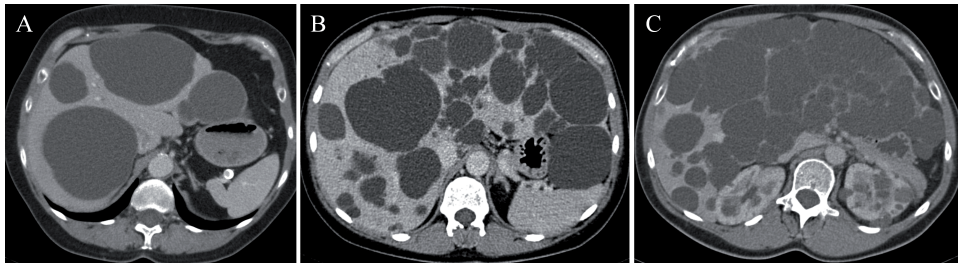


Figure 2: Gigot type I–III livers. A. Transverse CT image of Gigot type I cystic liver containing a couple of large (>10 cm) cysts, but <10 cysts in total. B. Transverse CT image showing a Gigot type II polycystic liver with diffuse involvement of liver parenchyma by multiple medium-sized cysts. C. Transverse CT image of a Gigot type III polycystic liver. The liver is completely occupied with numerous cysts, and only few areas of visible liver parenchyma are present.

Symptoms

The majority of PLD patients is clinically asymptomatic.[26] However, the massive hepatomegaly can cause compression of the adjacent gastrointestinal tract, vasculature, and diaphragm, resulting in mechanical symptoms. Frequent symptoms associated with PLD are abdominal distension, abdominal pain, dyspnea and back pain.[1, 29] In addition, the severe hepatomegaly can lead to malnutrition due to early satiety, anorexia and vomiting.[1, 37] In general, the capacity of the liver to synthesize proteins remains intact even in severe PLD.[38] Specifically in ADPKD, highly symptomatic PLD has become more common due to reduced cardiovascular mortality, extended renal survival, and increased life expectancy of patients on renal replacement therapy.[39-41] Complications of PLD include intracystic

haemorrhage, rupture of cysts or cyst infection and typically only occur in patients with severe PLD.[1, 42] Cyst haemorrhage and ruptures can be treated conservatively, whereas patients with infected cyst require hospitalization with intravenous administration of antibiotics.[43, 44] In rare cases, strategically located hepatic cysts can cause hepatic venous outflow obstruction, portal hypertension or obstructive jaundice.[1, 29, 45, 46] There are several generic questionnaires available that assess gastrointestinal symptoms in patients.[47-51] At this moment, there is no standard validated questionnaire that scores symptoms in PLD.

Therapy

Treatments options in PLD depend on the severity of the phenotype and on the presence of symptoms. If the phenotype is limited, PLD can be managed conservatively. The progression in most patients will necessitate a therapeutic intervention over time. In patients with dominant cysts percutaneous cyst aspiration and alcohol sclerosis is a good option.[34] In more advanced cases cyst fenestration[35], partial hepatectomy, and even liver transplantation may be indicated.[52] The choice of treatment depends on the extent, distribution, and anatomy of the cysts. So far, no preventive therapy exists for PLD. Several pharmacological options for PLD have been investigated. These drugs aim to reduce hepatic and renal volume, and in this respect somatostatin analogues appear to be the most promising.

Somatostatin analogues

The somatostatin analogues lanreotide and octreotide bind to somatostatin receptors 2, 3 and 5, which are widely expressed in many tissues including cholangiocytes.[53-55] To date, the exact spectrum of somatostatin receptor expression in polycystic liver epithelia is unknown. These long-acting agents reduce intracellular levels of cAMP by activating signalling cascades through the $G_i \alpha$ subunit, thereby inhibiting cholangiocyte proliferation and preventing fluid accumulation in liver cysts *in vitro* and *in vivo*. Indeed, in rats with inherited polycystic livers (PCK rats) octreotide treatment caused significant reductions in liver weight (-22%) and liver cyst volume (-39%), indicating that octreotide can suppress liver cyst growth.[55] In our center, we performed a trial with the long-acting somatostatin analogue lanreotide. In this multicenter, randomized, double-blind, placebo-controlled trial, we randomly assigned 54 patients with PLD to either lanreotide 120 mg or placebo, administered every 28 days for 24 weeks. Lanreotide reduced liver volume in PLD patients. Mean liver volume decreased from 4606 to 4471 mL with lanreotide, (-2.9%) while in placebo volume increased by 1.6%.[23] Two other studies demonstrated that 40 mg of long-acting octreotide monthly decreased liver volumes with 4.4% and 5.0% after respectively 6 and 12 months, whereas liver volume increased by 1.2% and 0.9% in the placebo arms.[24, 25] Side-effects of somatostatin analogues included steatorrhea, diarrhea, abdominal cramps and flatulence and were well tolerated in the trials. Although the effect of somatostatin analogues seems consistent between the trials, there was considerable variability in treatment response between included patients (Figure 3).

Gaps in our knowledge

The initial discovery by our group that somatostatin analogues decrease polycystic liver volumes has created a new field of therapeutic options in PLD (**Chapter 2**). However, there are still some issues that need to be resolved before somatostatin analogues can

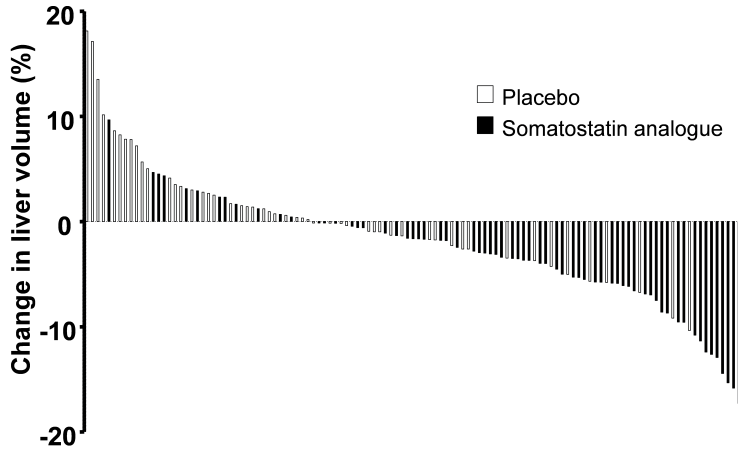


Figure 3: Percent changes in liver volume for all treatment periods including in the three placebo-controlled trials that evaluated somatostatin analogues in PLD. Each bar represents 1 treatment period (n=119).

be used in daily practice. A more pronounced side-effect profile can possibly off-set the potential benefits of somatostatin analogue therapy and thereby limiting its use in certain subgroups of PLD patients . In the same vein, the wide range of liver volume reductions in the clinical trials suggests there may be subgroups of patients with increased responses to somatostatin analogue therapy.[23] Given the expense involved and the overall modest effect of somatostatin analogues in trials, it is clear that we have to investigate whether there are subgroups of PLD patients who will benefit more from this therapy. We hypothesize that certain patient factors (age, gender), disease characteristics (underlying diagnosis, liver size, lab abnormalities) or treatment variables (somatostatin analogue type) may affect outcomes in PLD patients receiving somatostatin analogue therapy. By addressing these issues, we will identify factors associated with worse prognosis, lower occurrence of side-effects or with better treatment responses in PLD. These findings will help us to individualize treatment in PLD patients, thereby preventing unnecessary or ineffective somatostatin analogue therapy.

The aim of this thesis is to identify which patients with polycystic liver disease will benefit from somatostatin analogue therapy, in order to develop an individualized, evidence-based treatment approach for these patients. We composed two research questions in order to answer the aim of this thesis.

Research question 1: Are somatostatin analogues effective and safe in ADPKD patients?

Three randomized trials have demonstrated that somatostatin analogues decrease liver volume in mixed populations of patients with autosomal dominant polycystic kidney disease (ADPKD) and isolated PLD (described in more detail in **chapter 2**).[23-25] The chronic renal failure associated with ADPKD may influence the effect of somatostatin analogues and enhance the risk for adverse events. Our hypothesis is that the somatostatin

analogue lanreotide reduces total liver volume and total kidney volume, improves symptoms and health-related quality of life and has an acceptable safety profile in ADPKD patients. To investigate our hypothesis, we designed an observational trial that included 43 ADPKD patients with PLD. The primary outcome was change in total liver volume after 24 weeks of lanreotide therapy. Secondary outcomes were change in total kidney volume, renal function, gastrointestinal symptoms measured by the GIS and quality of life measured by the EuroQol-5D (EQ-5D).[56] We also include a standardized gastro-intestinal symptoms (GIS) questionnaire to assess the presence of gastrointestinal symptoms.[47] This questionnaire also included a visual analog scale (VAS) specific for abdominal pain. The EQ-5D is a health-related questionnaire that consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a health state assessment on a VAS scale (EQ-VAS). Each of the five dimensions can take one of three responses (no/some/severe limitations).[56] **Chapter 3a** describes the rationale and design of this trial, whereas **Chapter 3b** reports on the findings. We chose an observational design because it was not ethical to withhold a possible effective therapy from these symptomatic patients (principal of equipoise). Observational studies may be critiqued because they are thought to overestimate treatment effects. A formal study comparing outcomes of randomized and observational studies concluded that the latter study model neither over- nor underestimate treatment effects to any significant degree.[57] Although this design precluded direct comparison with untreated ADPKD patients, the results were directly applicable to clinical practice in real life.

Research question 2: Are there certain patient or disease groups with increased responses to somatostatin analogue therapy?

The large difference in individual responses to somatostatin analogues suggests that there are subgroups with increased response to somatostatin analogue therapy. We therefore performed an individual patient data meta-analysis including all trials that compared somatostatin analogues with placebo in PLD and had liver volume as the primary outcome.[23-25] The results of this study are discussed in **Chapter 4.** We hypothesize that the efficacy of somatostatin analogues on polycystic liver volume may vary in specific PLD subgroups based on underlying diagnosis, sex, age, and liver size. We chose to perform a meta-analysis on individual patient data, to achieve the highest grade of evidence. Indeed, study level meta-analyses may be adequate when estimating a singled pooled treatment effect or investigating study level characteristics, but they can lead to biased assessments and have limitations in explaining heterogeneity. Analyses of individual patients' data offer improved statistical power to investigate whether treatment effects are related to the patient.

In addition, the large variety in treatment responses makes it difficult to predict which patients have the most reduction in liver volume during somatostatin analogue therapy. By identifying patients that have a high chance for responding, we can spare other patients from undergoing unnecessary and costly somatostatin analogue therapy. We hypothesized that certain patient, disease or treatment characteristics predicted liver volume reduction in PLD patients receiving somatostatin analogue therapy. We pooled the individual patient data of 4 trials that investigated somatostatin analogues in patients with PLD. We included 153 patients that were treated with lanreotide 120 mg or

octreotide 40 mg for 6-12 months. Only patients with symptomatic or severe PLD were included, in order to represent the population that requires treatment in clinical practice. The results of this study are described in **Chapter 5**.

Finally, we completed the thesis by a general discussion and future perspectives in **Chapter 6**. This chapter summarizes our results and discusses the future role of somatostatin analogues in patients with PLD.

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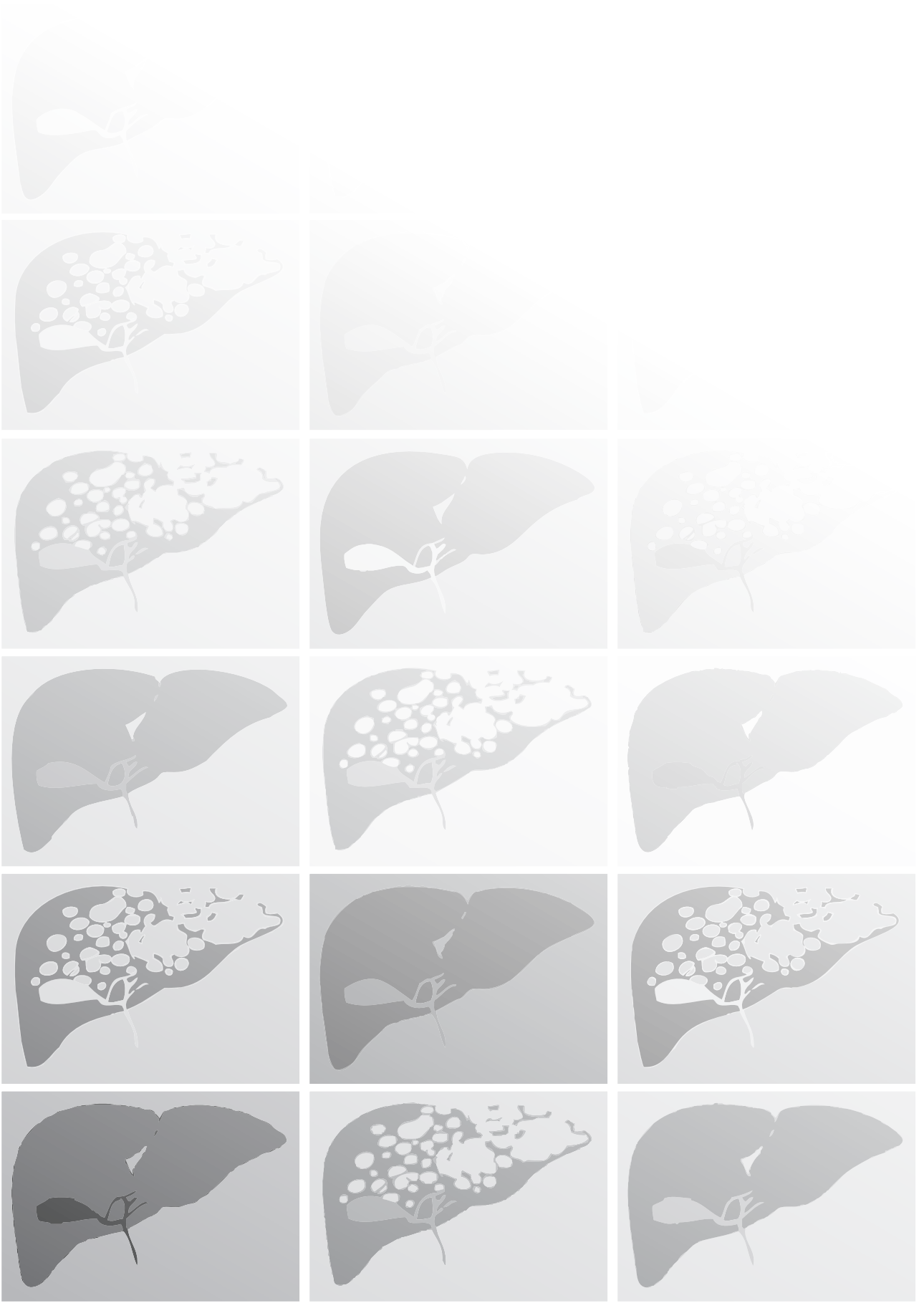

Chapter 2

Somatostatin analogues for treatment of polycystic liver disease

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Curr opin Gastroenterol. 2011; 27(3): 294-300

Abstract

Purpose of review
The present review summarizes the existing knowledge on polycystic liver disease and highlights the progress made in medical treatment for this condition in the past year.

Recent findings
Polycystic liver disease is associated with autosomal dominant kidney disease (ADPKD) and autosomal dominant polycystic liver disease (PCLD). Signaling pathways of adenosine 3',5' – cyclic monophospate (cAMP) and mammalian target of rapamycin (mTOR) are aberrantly regulated in polycystic livers and promote hepatic cystogenesis. Somatostatin analogues reduce intracellular cAMP, and this might prevent fluid accumulation in hepatic cysts. Several clinical trials published over the last year now show that somatostatin analogues when given for 6-12 months in patients with ADPKD and PCLD decrease total liver volume, attenuate polycystic kidney volume, and improve perception of health. In two recent studies mTOR inhibitors failed to halt the progression of ADPKD. It is still too early to recommend to start somatostatin analogues in polycystic liver disease and definitive answers should come from future clinical trials.

Summary
Somatostatin analogues are promising new medical drug options in the treatment of polycystic liver disease. However, more needs to be elucidated with regard to molecular mechanisms in hepatic cystogenesis, the uncertainty who will respond to therapy and long-term outcomes.

Introduction

Polycystic liver disease is a rare disorder arbitrarily defined by presence of more than 20 liver cysts.[1] It can be present in the combination with renal cysts as a manifestation of autosomal dominant polycystic kidney disease (ADPKD), or isolated in the absence of renal cysts as autosomal dominant polycystic liver disease (PCLD).[2] For a long time PCLD and ADPKD were assumed to be related phenotypic variants, but the discovery of causative genes led to the concept that they are genetically distinct.[3, 4] As observed in several trials, polycystic liver volumes vary from 1000 ml to over 10 000 ml.[5-7] Symptoms are related mainly to the size of the liver, and include abdominal distension, dyspnea, pain and early satiety.[1] Complications are uncommon and include bleeding, rupture and infection of cysts.[8] So far, no curative or preventive therapy exists for polycystic liver disease. Primary treatment goal in polycystic liver disease is reduction of total liver volume, as this is thought to relieve symptoms. Most current therapies are invasive and consist of surgical removal or at the minimum emptying of cysts.[9] Although these surgical techniques are fairly effective in treating patients with dominant cysts, their efficacy in management of advanced polycystic livers is only moderate.[8] Consequently, there is a clear need for other therapeutic options. In this article, we will review the advances in medical drug treatment of polycystic liver disease as to provide an update on latest developments.

Literature search

We searched the following electronic literature databases: clinicaltrials.gov, the Cochrane Central Register of Controlled Trials, and PubMed. All searches were limited to English language. We also checked the reference lists of included review articles. In electronic searches for efficacy trials, we used following MESH terms 'polycystic liver disease' OR 'ADPKD' OR 'PCLD'. All citations were imported into an electronic database (Reference Manager, ISI Researchsoft). The literature search was confined to articles published between July 2009 and January 2011. We identified a total of 322 articles that met the inclusion criteria. For the purpose of this review we primarily focused on articles addressing the role of medical therapy in management of polycystic liver disease.

Hepatic cystogenesis

Liver cysts arise from cholangiocytes and expand due to at least 3 different mechanisms: increased cell proliferation and apoptosis combined with neovascularisation; enhanced fluid secretion; and abnormal cell-matrix interactions.[10] These mechanisms are initiated by several signal transduction pathways that are aberrantly regulated in polycystic livers. Hepatic cysts exhibit markedly higher levels of phosphor-mammalian target of rapamycin (mTOR) and it downstream effectors which contributes to cholangiocyte proliferation and subsequent hepatic cyst expansion.[11] Furthermore, estrogens, insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) are overexpressed in hepatic cystic epithelium and promote proliferation of cholangiocytes in an autocrine manner.[12] Indeed, studies have shown that VEGF signaling pathways are activated in liver cyst epithelia and are capable of inducing the growth of cysts in mice, leading to the conclusion that VEGF inhibitors might be useful in inhibiting hepatic cystogenesis.[13, 14] Finally, adenosine

3',5' – cyclic monophospate (cAMP) acts as a second messenger in intracellular signal transduction and is involved in hepatic cystogenesis by multiple mechanisms. Alterations in cAMP stimulate cAMP-dependant chloride and fluid secretion from biliary epithelial cells and trigger cholangiocyte proliferation.[2] Moreover, secretin, the major cAMP agonist in cholangiocytes, stimulates the targeting and insertion of several transporters and channels into the apical membrane of cholangiocytes, thereby increasing fluid secretion.[2] This was supported by an elegant experiment demonstrating that intravenous secretin administration increases fluid secretion in hepatic cysts from ADPKD patients.[15] In view of its stimulatory effects on cell proliferation and fluid secretion, targeting cAMP production is a promising target for therapeutic intervention in polycystic liver disease.

Somatostatin analogues

Somatostatin is a naturally occurring gastrointestinal hormone that regulates various endocrine and exocrine processes.[16] The half-life of natural somatostatin is less than 3 minutes, thereby limiting its use in clinical practice. Synthetic somatostatin analogues with longer half-lives have been developed to overcome this disadvantage. Somatostatin and its synthetic analogues, such as lanreotide and octreotide, bind to somatostatin receptors 2, 3 and 5 and suppress intracellular cAMP by activating signaling cascades through the Gi protein. Furthermore, somatostatin decreases fluid secretion and cell proliferation by reducing cAMP in cholangiocytes.[17, 18] In addition, somatostatin blunts the release of cAMP agonist secretin.[19] In-vivo studies showed that octreotide reduces hepatic cyst volume and suppressed hepatic disease in rats by reducing cAMP.[10] As a consequence, somatostatin analogues are thought to be able to revert the process of hepatic cystogenesis by curtailing cAMP accumulation.

Human Studies

Several clinical observations support the use of somatostatin analogues in polycystic liver disease. The first cases describe the effect of somatostatin analogues in two patients with polycystic livers. A 3-month and 6-month therapy led to large reductions in liver volume in both patients (14.9 and 38.3%).[20] In line with these results, lanreotide 60 mg given monthly for 6 months in an ADPKD patient was accompanied by almost a 10% reduction in liver volume (Figure 1). Furthermore, another case-report documented that 12 months of octreotide in a patient with ADPKD reduced total hepatic and renal cyst volume by 6.3 and 8%.[21] Interestingly, a large cyst in the left breast from this patient also responded (-51%). This suggests that cyst fluid accumulation in different organs is a general, dynamic process which can be reversed by somatostatin analogues. A larger cases series in eight patients (seven ADPKD and one PCLD) with short-acting octreotide 100 µg three times a day subcutaneously for a median of 135 days resulted in a median 3.0% decrease in liver volume.[22] Unfortunately, due to absence of a control group, accurate comparison with the natural course of the disease was not possible.

These observational studies support the principle that somatostatin analogues are able to reduce liver volume in polycystic liver disease. However, these studies do not address the pertinent question how large the effect really is and which drug at which dosage should be used for which duration.

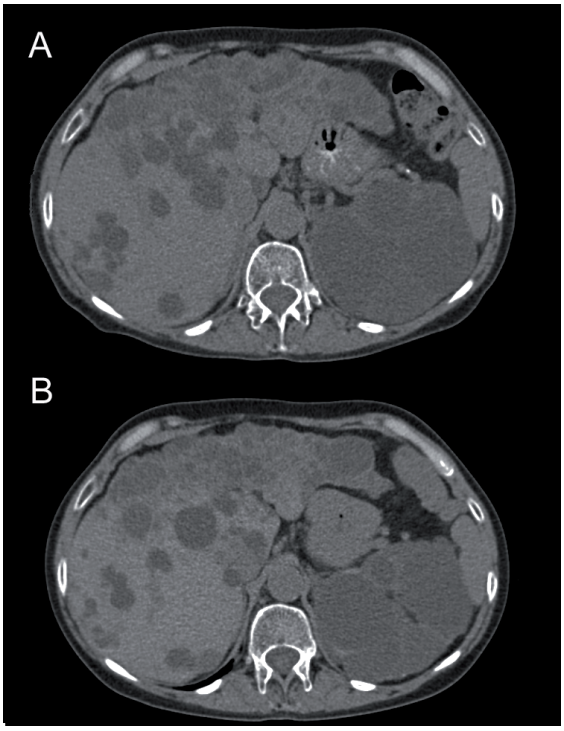

Figure 1: Reduction of liver volume following somatostatin therapy in an ADPKD patient. This picture shows an abdominal CT scan of an ADPKD patient who received lanreotide 60 mg for six months. Liver volume on panel A was 2.1L which decreased to 1.9L (panel B), a decline of almost 10%.

Clinical trials with somatostatin analogues

Encouraged by the results of the case studies mentioned above, researchers designed several randomized clinical trials to evaluate the effect of somatostatin analogues in polycystic liver disease (Table 1). All trials included patients with ADPKD or PCLD and used the difference in total liver volume as measured by computed tomography (CT) or magnetic resonance imaging (MRI) as a primary endpoint. The first trial treated 54 patients with severe polycystic livers as the result of ADPKD (n=32) of PCLD (n=22) with monthly injections of lanreotide 120 mg for 6 months. Liver volume decreased by 2.9% in the lanreotide group, but increased by 1.6% in the placebo group.[5] The volume reducing effect of lanreotide was also observed with other somatostatin analogues, for example octreotide. One trial evaluated the effect of long-acting octreotide 40 mg given monthly for a year in 42 patients with ADPKD (n=34) or PCLD (n=8).[6] The mean liver volume decreased by 5.0% in patients given octreotide, whereas in the placebo group liver volume remained practically unchanged (+0.9%). These results were supported by a post hoc analysis of data from a randomized, cross-over study in 12 patients with ADPKD.[26] In this analysis, octreotide 40 mg given monthly for 6 consecutive months reduced liver volume by 4.5%, whereas treatment with placebo resulted in 0.9% increase in liver volume.[7] Remarkably, this reduction with octreotide was fully explained by a reduction in parenchyma rather than cyst volume. However, no definite conclusions about the effect of octreotide on hepatic cyst volume can be drawn from this study, as baseline liver cyst volumes were very low. Collectively, these clinical trials raise a number of interesting implications: the beneficial effect is similar for patients with ADPKD and PCLD and larger livers had larger reductions with octreotide or lanreotide than smaller livers.

Table 1. Overview of characteristics and results of randomized controlled trials evaluating somatostatin analogue or mTOR inhibitor therapy in patients with ADPKD or PLCD

Study	Study drug	Design	Patient (n)	Study population	Treatment duration (months)	Treatment regimen	Primary End point	Mean baseline volume (ml)	change in baseline volume in treatment group (%)	change in baseline volume in placebo group (%)
Van Keimpema[5]	Lanreotide	RCT	54	ADPKD/PCLD	6	120 mg monthly	TLV change, CT	Liver: 4648 Kidney: 1058	Liver: - 2.9 Kidney: - 1.5	Liver: + 1.6 Kidney: + 3.4
Hogan[6]	Octreotide	RCT	42	ADPKD/PCLD	12	40 mg monthly	Percent TLV change, MRI	Liver: 5730 Kidney: 1030	Liver: - 5.0 Kidney: + 0.3	Liver: + 0.9 Kidney: + 8.6
Caroli[7]	Octreotide	randomized, crossover[a]	12	ADPKD	6	40 mg monthly	TLV change, CT	Liver: 1608 Kidney: 2435	Liver: - 4.5 Kidney: + 2.2	Liver: + 0.9 Kidney: + 5.9
Perico[23]	Sirolimus	randomized, crossover	15	ADPKD/PCLD	6	3 mg daily	TKV change, CT	Kidney: 1874	Kidney: + 2.2	Kidney: + 3.7
Serra[24]	Sirolimus	RCT	100	ADPKD	18	2 mg daily	Percent TKV, MRI	Kidney: 955[b]	Kidney: + 10.9	Kidney: + 9.7
Walz[25]	Everolimus	RCT	433	ADPKD	24	5 mg daily	TKV change, MRI	Kidney: 1968	Kidney: + 11.3	Kidney: + 15.8

[a] secondary post-hoc analysis performed on data of this crossover study; [b] volume in cm^3. RCT, randomized controlled trial; TLV, total liver volume; TKV, total kidney volume.

The dose of 120 mg lanreotide used in one study[5] was equivalent to 60 mg of octreotide, which was higher than the 40 mg of octreotide used in the other studies.[6, 7] However, as lanreotide has a lower affinity for the somatostatin receptor than octreotide, treatment doses were probably comparable between all trials.[27]

Renal Volume

Somatostatin analogues also have a positive outcome on polycystic kidneys in patients with ADPKD (Table 1). In one trial lanreotide reduced kidney volume by 1.5%, compared to 3.4% with placebo.[5] In contrast, trials that used octreotide showed slow polycystic kidney growth (0.3 and 2.2%) rather than volume reduction in comparison to placebo (8.6 and 5.6%).[6, 7] One trial reported that these observed effects on kidney volumes were strongly correlated to the change in liver volume.[7]

Side effects

Overall, treatment with somatostatin analogues is well tolerated. Most common side-effects are mild diarrhea with loose, pale stools and abdominal cramps, which appear after the first injections but disappear with prolonged use. Injections site granulomas were reported in patients receiving lanreotide or octreotide, with no occurrence in placebo groups.[5, 6] All patients considered the three times daily injection with octreotide regimen used in one trial as very intensive and difficult to continue, thus, the use of long-acting somatostatin is preferable.[22]

Perception of health

Two trials reported that the positive effect of somatostatin analogues was associated with a significant improved perception of general health.[6, 7] However, as pointed out in an accompanying editorial, the high frequency of gastrointestinal side-effects in somatostatin analogue treated patients may have compromised the actual blinding in this self-reported analysis.[28]

mTOR inhibitors

mTOR inhibitors have been used in renal transplant patients as a part of an alternative long-term immunosuppressive regimen and have strong anti-proliferative effects.[29] There is convincing preclinical data suggesting aberrant activation of the mTOR pathway in the pathogenesis of ADPKD.[30] Sirolimus, a mTOR inhibitor, reduces renal cyst growth, fibrosis

and proliferation in several different human-orthologous mouse models of polycystic kidney disease.[31-33] These observations set the stage for three clinical trials evaluating the effect of mTOR inhibitors on kidney volume in patients with ADPKD. The results of these trials, however, were disappointing (Table 1). A 2-year placebo-controlled trial evaluated whether everolimus, a mTOR inhibitor, would decrease total kidney volume in 433 patients with ADPKD with stage II or III chronic kidney disease.[25] While everolimus slowed the increase in total kidney volume, it did not slow the progression of renal impairment, indicating that decreasing kidney volume does not necessarily improve renal function. Another trial observed that 18 months of treatment with sirolimus in patients with early-stage ADPKD failed to slow renal enlargement.[24] In addition, a cross-over study compared the effect of 6 months sirolimus to conventional therapy on progression of ADPKD. This study showed no differences in kidney growth, although the study was too small to draw definite conclusions.[23] The latter two trials only included early-stage ADPKD patients, and no differences in renal function were observed between the two treatment arms. Unfortunately, none of these trials included a formal evaluation of liver size. It would be interesting to determine the effect of mTOR inhibitors on polycystic liver volume, as sirolimus given for 19.4 months in a series of 16 ADPKD patients following renal transplantation significantly reduced polycystic liver volume by 11.9%.[11]

mTOR inhibitor safety

The largest problem of mTOR inhibitors is the toxicity of the drug precluding its long-term use in a population that is relatively healthy and have few preexistent symptoms.[23, 34] In addition, the dose of sirolimus used in the trials above might be inadequate to achieve mTOR inhibition in cysts.[35] Limiting side-effects while achieving adequate inhibition of mTOR remains a challenge with mTOR inhibitor therapy.

Future therapeutic strategies

Other therapeutic strategies in polycystic liver disease are specific inhibitors of VEGF, IGF-1 or estrogens, as these growth factors promote cholangiocyte proliferation and hepatic cystogenesis.[12, 14] Furthermore, a recent study showed that pioglitazone, a PPARγ agonist, attenuates hepatic and renal cyst growth in a PCK rat model.[36] Finally, experimental evidence demonstrates that miRNAs (i.e., miR-15a) influence cholangiocyte proliferation and hepatic cyst growth by affecting the expression of the cell cycle regulator, Cdc25A.[37] These studies lay a framework for the development of new therapies aimed at preventing hepatic cystogenesis in patients with polycystic liver disease.

Strategies for the design of future clinical trials

There are still many questions to be answered. Little is known about the optimal dose of somatostatin analogues in treatment of polycystic liver disease. Somatostatin analogues are well tolerated, and higher doses may lead to more reduction in liver volume without an increase in frequency of side-effects. In addition, due to absence of long follow-up studies, it is still unknown how long the effects of somatostatin analogues will persist after treatment cessation. In a patient who received short-acting octreotide for 90 days, liver volume increased back to baseline at 3 months follow-up after a reduction of 9,4%, suggesting that long-term treatment is necessary.[22] It is now most important to determine

whether the long-term use of somatostatin analogues is safe and if the volume reducing effect is maintained by prolonged therapy. Experiments in a rat model suggested that the beneficial effects of octreotide are time-dependent and dose-dependent, indicating that longer duration of therapy might result in more substantial effects.[10] In addition, long-term studies in patients with acromegaly have shown that treatment with somatostatin analogues up to 4 years is well tolerated, suggesting that longer treatment with somatostatin is feasible.[38] Finally, individual patient factors that predict better treatment response should be explored. Currently, it is too early to recommend that patients with polycystic liver disease start with somatostatin analogues and these should only be used in clinical trials.

Ongoing future trials

There are several ongoing trials using somatostatin analogues in patients with polycystic liver disease (Table 2). The ALADIN trial (NCT00309283) evaluates the effect of long-acting somatostatin on kidney volume for 3 years in patients with ADPKD. Furthermore, we initiated a randomized, controlled trial (ELATE study, NCT01157858) to assess the effect of combined octreotide-everolimus therapy on liver volumes in symptomatic polycystic liver patients. These results will be available in 2011. As none of mTOR inhibitor trials estimated the effect on total liver volume, its role in polycystic liver disease still has to be elucidated.[23-25] Two trials (NCT01223755 and NCT01009957) are now ongoing to

Table 2: Most important ongoing clinical trials using somatostatin analogues or mTOR inhibitors in patients with ADPKD or PCLD

Study name	Study number	Study drug	Study population	Study design	Eligibility	Patients (n)	Treatment duration (months)	Primary end point	Completion Date
ALADIN trial	NCT00309283	Long-acting Somatostatin	ADPKD	Single center, randomized, single blind	Age > 18 GFR > 40	66	36	TKV change, MRI	June 2011
ELATE study	NCT01157858	Everolimus + Octreotide	PCLD	Single center, open label, randomized	Age 18 to 70 GFR > 60 Symptomatic	44	12	Percent TLV change, CT	December 2011
SIRENA-II	NCT01223755	Sirolimus	ADPKD	Single center, open label, randomized	Age > 18 GFR 15-40	40	36	GFR change (secondary end point, TKV/TLV, CT)	December 2013
PolEver	NCT01009957	Everolimus	ADPKD	Single center, open label, randomized	Age > 18 GFR 30-60	90	24	Reduction of GFR (secondary end point, liver cyst change, MRI)	December 2012

GFR, glomerular filtration rate; TKV, total kidney volume; TLV, total liver volume.

evaluate mTOR inhibitors in patients with ADPKD and use liver (cyst) volume change as a secondary endpoint (Table 2). However, the disappointing results of recently published trials on mTOR inhibitors in patients with ADPKD and its poor tolerability in this population clearly demonstrate that there is still a tough road ahead for the use of mTOR inhibitors in polycystic liver disease.

Conclusion

In summary, considerable progress toward alternative medical therapies for polycystic liver disease has been made. Several clinical trials have shown that it is possible to reduce polycystic liver volume and attenuate polycystic kidney volume with somatostatin analogues. In contrast, two recent studies evaluating the effect of mTOR inhibitors on polycystic kidney volume in ADPKD were not encouraging. It is paramount that well designed future studies in this field evaluate the efficacy of prolonging or combining

medical therapies in polycystic liver disease. In addition, further unraveling of molecular mechanisms in hepatic cystogenesis will aid in the identification of new therapeutic strategies.

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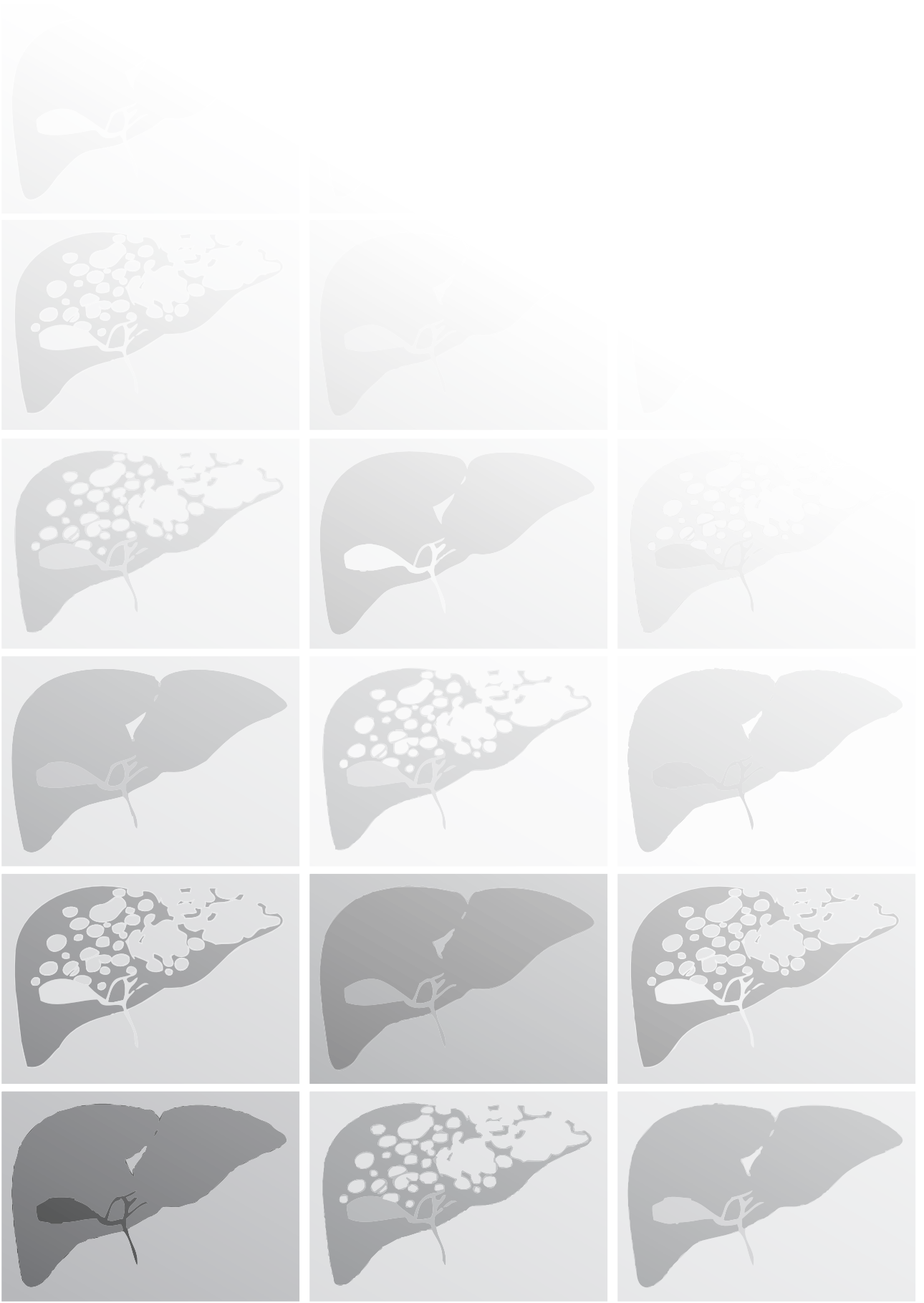

Chapter 3a

Rationale and design of the RESOLVE trial: lanreotide as a volume reducing treatment for polycytic livers in patiens with autosomal dominant polycystic kidney disease

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Abstract

Background
A large proportion of patients with autosomal dominant polycystic kidney disease (ADPKD) suffers from polycystic liver disease. Symptoms arise when liver volume increases. The somatostatin analogue lanreotide has proven to reduce liver volume in patients with polycystic liver disease. However, this study also included patients with isolated polycystic liver disease (PCLD). The RESOLVE trial aims to assess the efficacy of lanreotide treatment in ADPKD patients with symptomatic polycystic livers. In this study we present the design of the RESOLVE trial.

Methods/design
This open-label clinical trial evaluates the effect of 6 months of lanreotide in ADPKD patients with symptomatic polycystic livers. Primary outcome is change in liver volume determined by computerised tomography-volumetry. Secondary outcomes are changes in total kidney volume, kidney intermediate volume and renal function. Furthermore, urinary (NGAL, α1-microglobulin, KIM-1, H-FABP, MCP-1) and serum (fibroblast growth factor 23) biomarkers associated with ADPKD disease severity are assessed to investigate whether these biomarkers predict treatment responses to lanreotide. Moreover, safety and tolerability of the drug in ADPKD patients will be assessed.

Discussion
We anticipate that lanreotide is an effective therapeutic option for ADPKD patients with symptomatic polycystic livers and that this trial aids in the identification of patient related factors that predict treatment response.

Trial registration number
Clinical trials.gov NCT01354405

Background

Autosomal dominant polycystic kidney disease (ADPKD) most often presents a kidney phenotype with hypertension and renal failure due to continuous growth of renal cysts. It affects all ethnic groups and has an incidence of 1:500 to 1:1000. [1] ADPKD is inherited in an autosomal dominant fashion, and so far two genes, *PKD1* and *PKD2*, have been implicated to cause the disease.[2]

A large proportion of ADPKD patients suffers from polycystic liver disease, often while renal function capacity is preserved. [3] The natural course of polycystic liver disease dictates a continuous progression of size and number of hepatic cysts.[4, 5] The rate of progression is still unknown at his time, but recent trials showed that liver volume increases with 0.9-1.6% within one year.[6-8]

Most ADPKD patients with polycystic liver disease are asymptomatic until significant hepatomegaly develops. Subsequently mechanical complaints such as abdominal distension, pain, and early satiety arise.[9, 10] Other complications include intracystic hemorrhage or rupture of cysts causing acute abdominal pain. Currently available treatment options aim at reduction of liver volume and are mainly surgical.[11] However, drawbacks of surgical therapy are the partial effectiveness, their inherent morbidity and mortality and their inability to change the natural course of the disease.

This has led to the introduction of somatostatin analogues as a medical treatment option for polycystic liver disease. Somatostatin analogues, such as lanreotide and octreotide, are thought to decrease polycystic liver volume through their virtue of cAMP repression.[12, 13] We recently performed a trial with the somatostatin analogue lanreotide in polycystic liver patients with autosomal dominant polycystic liver disease (PCLD; isolated polycystic liver disease) or ADPKD.[8] In this trial, 54 patients were randomly assigned to lanreotide or placebo and treated for 6 months. Lanreotide decreased liver volume with 2.9%, while it increased by 1.6% with placebo. Moreover, there was a trend of delayed growth of polycystic kidney volume in the 32 ADPKD patients that participated. Others trials showed similar effects in reducing polycystic liver volume with octreotide.[6, 7, 14] These observations clearly support the thesis that polycystic liver volume can be reduced by somatostatin analogues.

However, the majority of these trials included a mixture of ADPKD and PCLD patients. It is still unknown if these patient groups have divergent responses to treatment with somatostatin analogues. To eliminate this possible confounding factor, we have designed and initiated a clinical trial (RESOLVE trial) to examine the effectiveness (change in total liver volume) of lanreotide in ADPKD patients with polycystic livers. In addition, we will determine the effect of lanreotide on change in total kidney and kidney intermediate volume. Intermediate volume is tightly correlated with glomerular filtration rate (GFR) and its long-term decline, and may represent a marker for ADPKD progression.[15] Finally, multiple sets of urinary (NGAL, α1-microglobulin, KIM-1, H-FABP, MCP-1) and plasma (fibroblast growth factor 23 (FGF23)) biomarkers have been discovered that are correlated to parameters of ADPKD disease severity, and may be associated with treatment response to lanreotide.[16, 17] In conclusion, using the dataset that is generated by the RESOLVE trial, we want to assess (1) whether lanreotide has a beneficial effect on growth of polycystic liver volume, (2) on growth of total kidney and intermediate volume, (3) on renal function, and (4) whether the suggested biomarkers predict treatment responses to lanreotide.

Methods/design

Study aim
The primary objective of the RESOLVE trial is to determine the effectiveness of lanreotide to attenuate growth of liver volume in ADPKD patients with symptomatic polycystic livers. ADPKD patients with polycystic livers will receive lanreotide 120 mg every 4 weeks for a total of 24 weeks (Figure 1). Secondary objectives are to assess the effect of lanreotide treatment on total kidney and kidney intermediate volume, to follow renal function and to identify biomarkers that predict treatment response. Finally, safety and tolerability of lanreotide treatment in ADPKD patients will also be assessed.

Study population
ADPKD patients with symptomatic polycystic liver disease Gigot type II (diffuse medium-size cysts; hepatic parenchyma preserved) or Gigot type III (massive, diffuse small- and medium-size cysts; little hepatic parenchyma preserved) between 18 and 70 years are eligible for participation of the study.[18] Symptomatic patients are defined as having at least three of the following symptoms:

- Abdominal pain
- Abdominal distension
- Abdominal fullness
- Dyspnoea
- Early Satiety
- Back pain
- Nausea or vomiting
- Anorexia
- Weight loss
- Jaundice

The diagnosis of ADPKD is based upon the Ravine criteria.[19] Furthermore, patients must have an estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) above 30 ml/min/1.73 m^2.[20] The specific study inclusion and exclusion criteria are listed below.

Inclusion criteria:

- Age 18 to 70 years
- Adult subjects with a diagnosis of ADPKD and at least a symptomatic polycystic liver Gigot type II [18]
- eGFR > 30 ml/min/1.73m^2 (MDRD formula) at screening
- Subjects are willing and able to comply with the study drug regimen and all other study requirements
- Signed informed consent

Exclusion criteria:

- History of renal transplantation
- Use of oral contraceptives or estrogen suppletion
- Pregnancy or breastfeeding

- History of cardiac or pulmonary disease, symptomatic gallstones, pancreatitis or diabetes mellitus
- Intervention (aspiration or surgical) targeted at hepatic or renal cysts within three months of baseline
- Treatment with somatostatin analogues within 3 months of baseline
- Mental illness that interferes with the patient ability to comply with the protocol
- Drug or alcohol abuse within one year of baseline
- Increased liver enzymes (2-fold above normal values); exception is an isolated elevated gamma-glutamyltransferase or alkaline phosphatase, which occurs frequently in polycystic liver disease
- Co-medication with known interaction with lanreotide, like cyclosporine

Exclusion criteria for the use of iodine based radiocontrast:

- Use of nephrotoxic agents like NSAIDs or diuretics within 24 hours before receiving a contrast-enhanced CT-scan
- History of moderate or severe reaction to contrast injection
- History of contrast induced nephropathy
- Treatment with I131 during the course of the trial
- Diagnosis of Morbus Kahler or Morbus Waldenström
- eGFR < 60 ml/min/1.73m2 (MDRD formula)

Study design and setting

The RESOLVE trial is a single centre open label study in subjects with ADPKD. The trial aims to enroll 43 ADPKD patients. The trial design is schematically represented in Figure 1. All eligible patientsreceive lanreotide 120 mg for a total of 24 weeks. At start and end of treatment, total liver and kidney volumes are measured by computer-tomography (CT) with contrast media if eGFR (MDRD) is > 60 ml/min/1.73 m2, or without contrast media if eGFR (MDRD) is 30–60 ml/min/1.73 m2. In addition, all patients are evaluated at 4 and 12 weeks after start of treatment. Recruitment has started in July 2011, will last until July 2012 and will be completed by July 2013. This study is submitted to clinicaltrials.gov (NCT01354405).

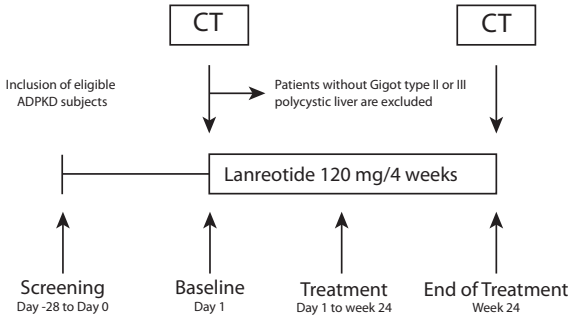

Figure 1: RESOLVE trial profile. ADPDK subjects are screened for eligibility, and 43 ADPKD patients with symptomatic polycystic liver disease and eGFR > 30 ml/min (MDRD formula) will be included. At day 1, all patients undergo CT volumetry of liver and kidneys. Patients without polycystic type II or III livers, as determined with CT volumetry, will be excluded from the study. Interval visits are scheduled 4 and 12 weeks after start of treatment. After 24 weeks of treatment with lanreotide (6 injections), another CT will be erformed to evaluate the change in liver and kidney volume

Trial treatments

All patients will receive long-acting 120 mg Somatuline® (Lanreotide) administered deeply subcutaneously every 4 weeks (28 days for a total duration of 24 weeks). Another trial documented the efficacy and safety of administration of 120 mg lanreotide in patients with polycystic liver disease and demonstrated that this dosage is well tolerated in patients and there were no notable drop-outs.[8] The most common adverse effect are loose, pale and fatty stools which typically start 24 hours after the first injection of lanreotide and lasts for 1–4 days. Pancreas enzyme replacement is prescribed to ameliorate these symptoms if they persist. In case of lanreotide-associated toxicity, the dose will be reduced with 30 mg until symptoms disappear. Lanreotide will be administered at the patient's home by a dedicated nursing team.

Primary outcome

The primary outcome of the RESOLVE trial is to assess the effect of lanreotide treatment on total liver volume in ADPKD patients with symptomatic polycystic liver disease. Primary efficacy endpoint is absolute change in liver volume after 24 weeks of treatment with lanreotide compared to baseline liver volume. We compare our findings with the natural course of polycystic liver growth observed in the trials that evaluated somatostatin analogue treatment in PLD patients.[6-8]

Secondary outcomes

The proportional change in liver volume (normalized as percentage) from inclusion to week 24 will be assessed as a secondary outcome. Furthermore, other secondary outcomes are the change in total kidney volume and that of 3 kidney tissue classes.[15] We will distinguish 3 kidney tissue classes on basis of CT images: cysts, parenchyma, and intermediate volume. Intermediate volume represents regions with contrast enhancement markedly lower than that of vascularized parenchyma tissue but higher than that of cysts, and is correlated to GFR decline.[15, 21] In addition, changes in quality of life (assessment with EuroQoL questionnaire) and gastro-intestinal symptoms (using a gastrointestinal symptoms questionnaire) will be measured at baseline and at end of treatment.[22, 23] Renal function will be assessed by using estimation equations (MDRD and cystatin C) as well as measured creatinine clearance determined by 24-hour urine collection. The frequency and severity of all reported adverse events will be recorded at every visit to evaluate the safety and tolerability of treatment with lanreotide. Finally, urinary biomarkers (NGAL, α1-microglobulin, KIM-1, H-FABP, MCP-1) and serum FGF23 will be assessed before and after treatment with lanreotide.[16, 17] These biomarkers are correlated to parameters of ADPKD disease severity and may predict treatment response to lanreotide. As concentration of FGF23 in serum is dependent of vitamin D, parathyroid hormone (PTH), calcium and phosphate serum levels, these parameters will also be measured at start and end of treatment.

Data collection

Data will be collected into a case record form designed to capture all visit information including medical history, results from laboratory analysis and adverse events. Study duration for all patients is 25–28 weeks in total, divided in a 1–4 weeks screening phase and a 24 weeks follow up phase after start of lanreotide (Figure 1). At screening, a

pregnancy test is performed (for women with childbearing potential). Within the follow up phase of the trial, patients are seen at week 0, 4, 12 and 24. During each visit, medical history, adverse events, tolerability and drug accountability are assessed. In addition, vital signs and weight are measured, blood samples are drawn and the eGFR (MDRD) is estimated. Two main study visits including CT volumetry (procedure described below), questionnaires, 24 hour and spot urine collection will take place at start (week 0) and end of treatment (week 24). Furthermore, blood and urine samples will be taken for assessment of serum FGF23, PTH, Vitamin D, Cystatin C and the urinary biomarkers. The requested parameters at the different visits are listed below.

Screening

- Written informed consent
- Eligibility criteria check
- Estimated GFR (MDRD)
- General characteristics
- Concomitant therapy and medical history
- Physical examination and vital signs
- Laboratory tests: hematology, biochemistry and lipid profile
- Pregnancy test in females between 18-50 years

Baseline (week 0) and end-of-treatment (week 24)

- CT liver and kidney volumetry
- Estimated GFR (MDRD and Cystatin C clearance)
- Creatinine (24-hour urine)
- Urinary biomarkers: NGAL, α1-microglobulin, KIM-1, H-FABP, MCP-1 and creatinine (spot urine)
- FGF23 (serum and spot urine)
- Vitamin D, PTH, calcium and phosphate (serum)
- GI symptom questionnaire
- EuroQol questionnaire

Every visit

- Adverse events and concomitant therapy
- Drug accountability
- Physical examination and vital signs
- Weight
- Estimated GFR (MDRD)
- Laboratory tests: hematology, biochemistry and lipid profile

CT Scanning and 3-Dimensional Volumetry

CT scans at baseline and week 24 will be performed on a multidetector CT scanner (Somatom Sensation 16 or 64; Siemens Medical Solution AG, Erlangen, Germany). All CT scans are blinded to patient identity and date of birth as well as date of scan. The effect of lanreotide will be evaluated by 3D total liver and kidney volume measurement of CT scan slices using Pinnacle3® version 8.0 g (Philips, Eindhoven, The Netherlands). Imaging protocol includes that CT scans have a slice thickness of 3 mm, and liver and

separate kidneys will be outlined manually every 9 mm. The software interpolates the intermediate slices and calculates the areas within the indicated circumference, and finally, total liver or kidney volume. The vessels and the ureter in the area of the renal hilum are excluded from manual volumetric marking. Unblinding of CT scans will be performed after all liver and kidney volumes are measured.

Intermediate volume identification on CT images
Intermediate volume will be assessed as described earlier.[21] Briefly, the kidneys will be outlined manually on all acquired digital images using interactive image editing software (GIMP; GNU Image Manipulation Software, www.gimp.org). Subsequently, as an image enhancement step, anisotropic diffusion filtering will be used to smooth high-frequency noise. [21] Binary masks generated from the image outlines will be applied to the enhanced images, and image segmentation will be applied to the resulting kidney regions using a statistical approach known as Otsu's thresholding.[24] After the application of Otsu's method with a number of classes equal to 4, each voxel in the volume will classified as fat, cyst, intermediate, or parenchyma. From the segmented images, cyst, intermediate, and parenchymal volumes will be computed by multiplying the voxel count of each class by voxel volume, as determined by the acquisition protocol.[21] Validation of the segmentation procedure is described previously.[21]

Study withdrawal
Patients will be withdrawn from the study for any of the following reasons: withdrawal of informed consent, pregnancy, failure to adherence to protocol requirements, unacceptable toxicity, surgical intervention during the trial and if the investigators conclude that it is in the patient's best interest for any reason. There will be no option of replacement into the study after withdrawal.

Sample size considerations
A previous trial suggested that 6-month treatment with lanreotide induced a 134 ml decrease in total liver volume in polycystic liver patients.[8] For the purpose of this study we assumed that lanreotide is able to resort in a similar effect in patients with exclusively ADPKD. A sample size of 39 will achieve 80% power to detect a difference of 150.0 mL (SD 325.0 ml) in liver volume (pre versus after treatment) using a two-sided α-level of 0.05. Taken into account a dropout rate of 10%, the sample size has to be 43 for the complete cohort.

Statistical analysis
All outcomes will be analyzed on an intention-to-treat basis. Parallel analyses conducted on per-protocol population will be performed. The volume of the liver will be determined as mentioned before. For primary and secondary endpoints, absolute and relative differences between baseline and end of treatment will be analyzed using a paired two-sided t-test, or Wilcoxon ranked sum test where appropriate. All statistical analyses will be two-sided with a critical significance level of 5%.
To evaluate which biomarkers predict treatment response to lanreotide, the association between each biomarker (NGAL, α1-microglobulin, KIM-1, H-FABP, MCP-1 and FGF23) and each of the primary and secondary outcomes will be examined by univariate linear

regression analyses. Predictors that are univariately associated with the outcome (*p*-value < 0.10) will be included in multivariate linear regression analyses. The model will be reduced by excluding predictors from the model with a *p*-value of > 0.05. In addition, the following variables will also be included in univariate models as predictors of favorable outcome as a secondary analysis: age, baseline liver volume, baseline kidney volume, kidney intermediate volume and estimated renal function (MDRD and cystatin C). All abnormal laboratory results will be listed and frequency tables will be compiled for Adverse Events classified according to the standard WHO-ART Body System Dictionary and preferred terms.

Ethical considerations

Ethical approval has been obtained from the local ethics committee of the Radboud University Nijmegen Medical Center. This study will be performed in accordance with the protocol, the guidelines of Good Clinical Practice/ICH, the principles of the Declaration of Helsinki 1964 as modified by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 including two notes of clarification paragraph 29 and 30, and the local national laws governing the conduct of clinical research studies. All subjects have the right to withdraw from the study at any time during the trial. Safety of trial subjects is monitored by an independent data safety monitoring board (DMSB).

Discussion

Treatment with lanreotide may results in several identifiable benefits for ADPKD patients with polycystic liver disease. It may map the road to a causal therapy for patients with polycystic liver disease. Current surgical procedures carry the risk of considerable morbidity and not all patients are qualified for this approach. Alternative options are needed and our trial will establish whether and to which extent and in whom lanreotide treatment can reduce liver volume growth in ADPKD.

The main strength of the RESOLVE trial is to determine whether lanreotide decreases liver volume in patients with ADPKD. Another group performed a post-hoc analysis of data from a randomized, cross-over study in 12 patients with ADPKD. [5] In this analysis, they evaluated the effect of octreotide in 12 ADPKD patients with polycystic livers and found a beneficial effect on liver volume.[6] However, these findings must be taken with caution due to the small sample size and because carry over effects cannot be excluded given the cross-over design. This will be the first trial that is powered to detect a small but significant change in polycystic liver volume in ADPKD patients treated with lanreotide. Furthermore, although we predetermined renal volume and renal function as a secondary outcome, the inclusion of exclusively ADPKD patients allows us to evaluate an effect of lanreotide on kidney volume and function. Third, intermediate volume is tightly connected to the decline in GFR and might be useful as a marker for ADPKD progression.[15] In this trial, we will investigate whether lanreotide has a beneficial effect on intermediate volume. Fourth, it is still unknown which patient factors predict treatment response to somatostatin analogues. Urinary and serum biomarkers associated with ADPKD disease severity are assessed in the RESOLVE trial at baseline and at end of treatment.[16, 17] We hope to correlate these markers to treatment response as this will allow us to give evidence based recommendations which ADPKD patients will benefit specifically from

treatment with lanreotide. Finally, this design provides an opportunity to study the safety of lanreotide in ADPKD patients with symptomatic polycystic liver disease.

There are limitations that come with our study worth addressing. First, as we seek polycystic liver targeting, ADPKD patients with symptomatic polycystic livers and only mildly enlarged polycystic kidneys are not excluded from the RESOLVE trial. To properly evaluate the effect of lanreotide on polycystic kidney volume, we should have introduced a minimal threshold of total kidney volume. Second, we do not include a control arm in our trial, but rather sought comparison with values at baseline. This prevents us from direct comparison with untreated ADPKD patients. However, based on our observations and the data from placebo arms of other randomized clinical trials, it is possible to establish the natural course of symptomatic polycystic liver disease. In our original trial, an increase of 1.6% in liver volume was observed after 6 months, while in another trial liver volume increased with 0.9% after 12 months.[7,8] Both these trials included a mixture of APDKD and PCLD patients. Liver volume increased with 1.2% during 6 months in a third trial that included exclusively ADPKD patients.[6] As the natural growth pattern of polycystic liver disease does not seem to differ between ADPKD and PCLD, we may use the data from these placebo arms to evaluate if lanreotide affects the growth of polycystic liver volume. In addition, the lack of a control group guarantees that a possible effective therapy is not withheld from symptomatic PLD patients included in the trial, and that the results will be directly applicable to ADPKD patients in the daily practice.

Despite these limitations, our study will add valuable information to the literature of medical treatment of polycystic liver disease.

In conclusion, by designing the RESOLVE trial, we anticipate that lanreotide is an effective therapeutic option for ADPKD patients with symptomatic polycystic livers, and we hope to identify patient related factors that predict treatment response.

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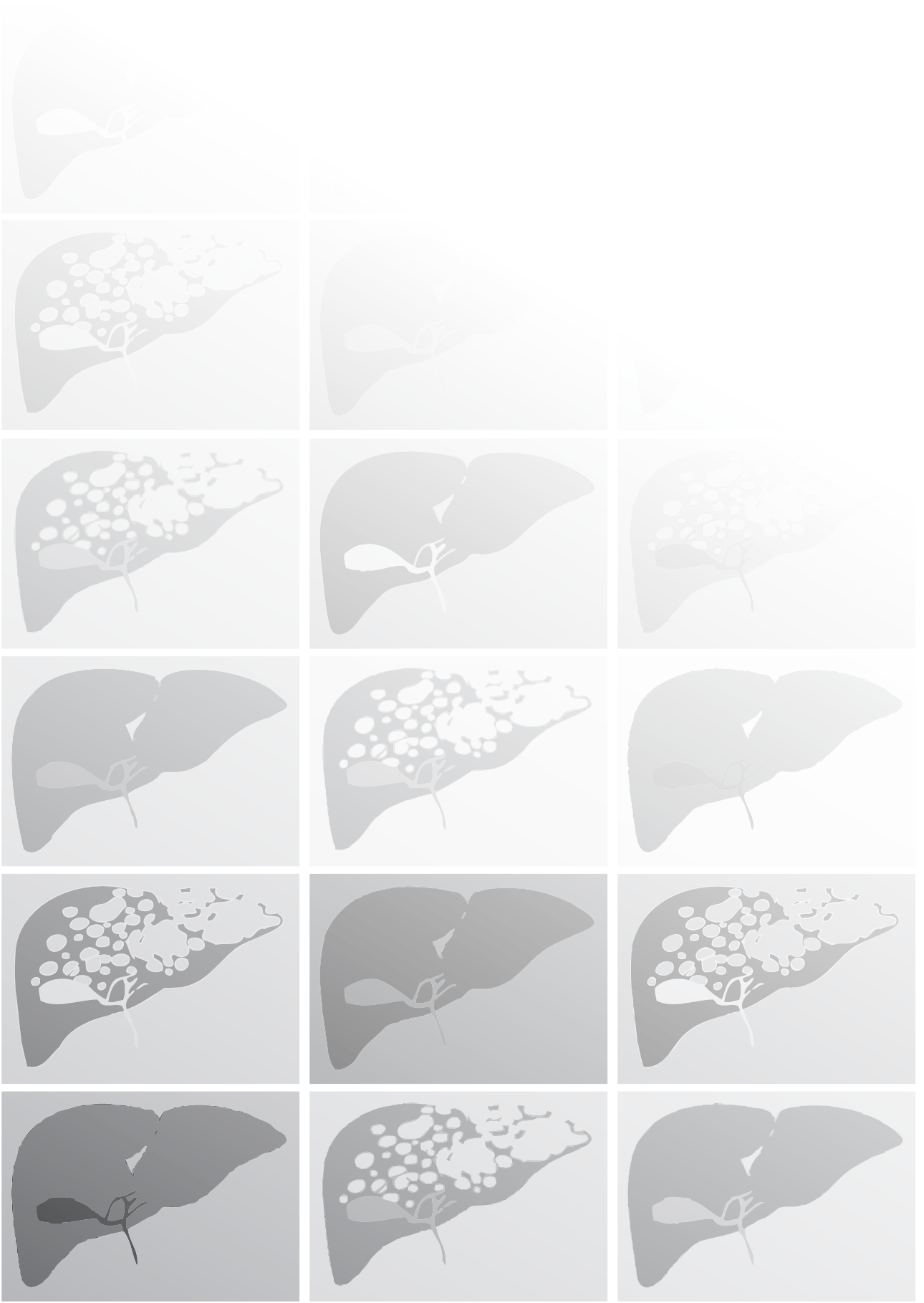

Chapter 3b

Effect of lanreotide on polycystic liver and kidneys in autosomal dominant polycystic kidney disease: an observational trial

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Abstract

Background & Aim
Several trials have demonstrated that somatostatin analogues decrease liver volume in mixed populations of patients with autosomal dominant polycystic kidney disease (ADPKD) and isolated polycystic liver disease. Chronic renal dysfunction in ADPKD may affect treatment efficacy of lanreotide and possibly enhances risk for adverse events. The aim of this open-label clinical trial (RESOLVE trial) was to assess efficacy of 6 months lanreotide treatment 120 mg subcutaneously every 4 weeks in ADPKD patients with symptomatic polycystic liver disease.

Methods
Primary outcome was change in liver volume after 6 months, secondary outcomes were changes in kidney volume, eGFR, symptom relief and health-related quality of life (Euro-Qol5D). We excluded patients with an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2. We used the Wilcoxon signed-rank test or paired two-sided t-test to analyze within-group differences.

Results
We included 43 ADPKD patients with polycystic liver disease (84% female, median age 50 years, mean eGFR 63 ml/min/1.73m^2). Median liver volume decreased from 4,859 ml to 4,595 ml (-3.1%;p<0.001), and median kidney volume decreased from 1,023 ml to 1,012 ml (-1.7%;p=0.006). eGFR declined 3.5% after the first injection, remained stable up to study end, to decline again after lanreotide withdrawal. Lanreotide significantly relieved postprandial fullness, shortness of breath and abdominal distension. Three participants had a suspected episode of hepatic or renal cyst infection during the study.

Conclusion
Lanreotide reduced polycystic liver and kidney volumes and decreases symptoms in ADPKD patients. Moreover, eGFR decreased acutely after starting lanreotide, stabilized thereafter and declined again after withdrawal.

Background

A subset of patients with autosomal dominant polycystic kidney disease (ADPKD) develops significant hepatomegaly due to polycystic liver disease.[1-4] Subsequently mechanical complaints may arise in this specific subgroup of patients and compromise quality of life.[5, 6] Although surgical therapies may be successful in reducing liver volume in selected patients, they are only partial effective, cause significant morbidity and mortality, and most importantly, are unable to change the natural course of the disease.[7-9]
Somatostatin analogues, including lanreotide and octreotide, are thought to decrease polycystic liver volume through their ability to reduce cAMP.[8, 10] In the last few years, several trials have demonstrated the liver and kidney volume reducing effects of lanreotide and octreotide in patients with isolated polycystic liver disease and ADPKD.[11-15] Moreover, a recent meta-analysis showed that 6-12 months of somatostatin analogue therapy decreased polycystic liver volume with 5.3% in polycystic liver disease patients when compared to placebo.[16] These observations clearly support the thesis that growth of polycystic liver and kidneys can be suppressed by somatostatin analogues.
However, these studies included a diverse population of patients with or without cystic kidneys. It is possible that chronic renal dysfunction in ADPKD affects treatment efficacy of lanreotide and possibly enhance risk for adverse events. In addition, the aforementioned trials also included patients without symptoms related to their enlarged liver, which complicates assessment of treatment response.
To eliminate these possible confounding factors, we have designed and initiated an observational trial to examine the efficacy of lanreotide in reducing liver and kidney volumes in ADPKD patients with symptomatic polycystic liver disease. We also determined the effect of lanreotide on renal function, gastrointestinal symptoms and health-related quality of life.

Methods/design

A detailed protocol of the study procedures has been described elsewhere. A brief caption follows below.[17]

Study population
Symptomatic ADPKD patients with polycystic livers (Gigot type II or III) were eligible for study participation.[18] Inclusion criteria were age between 18 and 70 years and an estimated glomerular filtration rate (eGFR) above 30 ml/min/1.73m^2 using the abbreviated Modification of Diet in Renal Disease Study equation (MDRD).[19] Symptomatic patients were defined as ECOG-Performance scale ≥ 1 and three or more of the following symptoms: abdominal pain/distension/fullness, dyspnoea, early satiety, back pain, nausea/vomiting, anorexia, weight loss and jaundice. ADPKD diagnosis was based upon the modified Ravine criteria.[20] Major exclusion criteria were renal transplantation; oral contraceptives or estrogen substitution; surgical intervention targeted at liver or kidneys or somatostatin analogue treatment within 3 months before baseline.

Study design and setting
This observational trial was performed at the Radboudumc, Nijmegen, the Netherlands

from May 2011 until April 2013. All patients received long-acting lanreotide (Somatuline®, Ipsen, Boulogne Billancourt, France) 120 mg subcutaneously every 4 weeks for a total of 24 weeks and received a CT at baseline and end of treatment. Lanreotide was administered At patient's homes by independent nurses.

Outcome measures

Primary outcome of this trial was change in total liver volume (TLV) after 24 weeks of treatment with lanreotide compared to baseline, as determined by CT volumetry. Secondary outcomes were change in total kidney volume (TKV), as determined by CT volumetry; change in eGFR; change in creatinine clearance, as determined by 24-hour urine collection; change in gastrointestinal symptoms, as assessed by the gastrointestinal (GI) symptoms questionnaire; and change in health-related quality of life, as assessed with Euro-QoL (EQ-5D) questionnaire, all measured at the same time points. eGFR was assessed by using creatinine-based estimation equations, the 4-variable MDRD formula[19] and chronic kidney disease epidemiology collaboration formula (CKD-EPI).

The GI symptoms questionnaire assesses type and severity of 11 symptoms on a 7-point adjectival scale, and uses a visual analogue score (VAS) to measure abdominal pain.[21] The EQ-5D consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a health state assessment (EQ-VAS). Each of the five dimensions can take one of three responses (no/some/severe limitations).[22] We dichotomized GI and EQ-5D questionnaire scores for absence or presence of symptoms/limitations. Finally, frequency and severity of all reported adverse events were recorded at every visit to evaluate the safety and tolerability of lanreotide therapy.

CT Scanning and 3-Dimensional Volumetry

CT scans at baseline and week 24 were performed with a multidetector CT scanner (Toshiba Aquilion-one, Toshiba Medical Systems, Zoetermeer, The Netherlands). All CT scans were blinded to patient identity, date of birth and date of scan. The effect of lanreotide was evaluated by 3D total liver and kidney volume measurement of CT scan slices using Pinnacle$^{3®}$ version 8.0h (Philips, Eindhoven, The Netherlands).[17] Unblinding of CT scans was performed after all liver and kidney volumes were measured by two independent researchers (TG&JH). To warrant limited measurement bias, the interobserver variability was assessed in a set of 8 CT scans using a Bland-Altman plot. The Bland-Altman plot showed a mean difference of -0.4±0.6% between the two researchers that performed CT volumetry, indicating excellent agreement.

Statistical analysis

Based on a previous trial, we expected that 6 months of lanreotide treatment induced a mean difference of 150 ml (standard deviation 325 ml) in TLV in ADPKD patients.[14] Based on these assumptions a sample size of 39 will achieve 80% power to detect this expected difference in liver volume (pre versus after treatment) using a two-sided α-level of 0.05. Taken a dropout rate of 10% into account the sample size for this trial was 43.

All primary and secondary outcomes were calculated according to the intention-to-treat principle. Patients who dropped out the trial before end of treatment (24 weeks after baseline) received a preliminary end-of-treatment CT scan for the benefit of the intention-to-treat analysis. In addition, for patients without an outcome at end-of-treatment, we

used the 'last observation carried forward' method to impute missing data. We calculated means±standard deviations or medians with interquartile ranges (IQR) for normally or non-normally distributed data respectively. As liver and kidney volumes have a skewed distribution, we used the Wilcoxon signed-rank test to analyze within-group differences. Within-group differences were analyzed using the paired two-sided t-test for the other secondary endpoints. Associations between TLV and TKV changes were evaluated by Spearman's correlation test. McNemar's test was used to compare paired dichotomized outcomes. All statistical analyses were two-sided with a significance level of 5% and were performed with SPSS statistical software package version 20.0 (SPSS Inc., Chicago, IL).

Ethical considerations
Ethical approval was obtained from the local institutional review board (IRB), the committee human research region Arnhem-Nijmegen (CMO Arnhem-Nijmegen). This study was performed in accordance with the protocol, guidelines of Good Clinical Practice/ICH and the principles of the Declaration of Helsinki 1975. Safety of trial subjects was monitored by an independent data safety monitoring board. We obtained patient consent from every included participant.

Results

Fifty-one ADPKD patients were assessed for eligibility to participate in the trial (Figure1). Reasons for exclusion were eGFR < 30 ml/min/1.73m^2 (n=4), an autosomal dominant polycystic liver disease diagnosis (n=3) or absence of polycystic liver disease on CT (n=1). Finally, we assigned 43 ADPKD patients with polycystic liver disease (mean eGFR 63 ml/min/1.73m^2) to treatment with lanreotide. Baseline characteristics are shown in Table1.
One patient underwent double-J ureteral stent placing of the right kidney during the trial, which beneficially affected renal outcomes at end of treatment. Therefore, we used this patient's baseline data to impute renal data at end of therapy, for the benefit of the intention-to-treat analysis. A total of 42 patients (98%) completed the full 24-week treatment period, as one patient withdrew consent 16 weeks after baseline due to decreasing eGFR. This patient received a premature end-of-treatment CT scan.

Liver volume
Median TLV decreased from 4,859 mL (IQR 3,110-7,822 mL) at baseline to 4,595 mL (IQR 3,172-7,910 mL) in the 43 ADPKD patients treated with lanreotide, which is an average reduction of -3.1±4.6% (Figure2A). The difference in TLV was statistically significant (-187 mL;p<0.001) using the Wilcoxon signed-rank test (supplementary Figure1). The majority of patients (84%) responded with a decrease in liver volume.

Kidney volume
In the 43 lanreotide-treated patients, median TKV declined from 1,023 mL (IQR 619-2,365 mL) to 1,012 mL (IQR 597-2,378 mL), with an average decrease of -17 mL (p=0.006). This corresponds with a mean decrease of -1.7±3.4% (Figure2B; supplementary Figure1). Two-third of patients (67%) showed a reduction in total kidney volume.
Changes in TLV and TKV were weakly correlated (r=0.37;p=0.01).

Table 1: Baseline demographic, clinical, and laboratory characteristics of 43 included patients

Age (y)	51±9
Gender	
Female	36 (84)
Male	7 (16)
Liver volume (ml)	4859 (3110 – 7822)
Kidney volume (ml)	1023 (619 – 2365)
eGFR (ml/min/1.73m^2)	63±17
Creatinine clearance (ml/min)[a]	79±24
Weight (kg)	74 (67 – 83)
BMI (kg/m^2)	26 (23 – 28)
SBP (mmHg)	129 (120 -141)
DBP (mmHg)	82 (72 – 88)
Current blood pressure lowering medication	33 (77)
Angiotensin-converting-enzyme inhibitor, angiotensin-receptor blocker, or both	30 (70)
History of renal cyst infection	3 (7)
History of hepatic cyst infection	4 (9)

Data are reported as median (interquartile range), mean ± standard deviation or absolute numbers (%). eGFR is estimated by the abbreviated MDRD equation. eGFR, estimated glomerular filtration rate; BMI, Body Mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure. [a]Determined by 24-h urine collection.

Renal function

Mean eGFR (MDRD equation) decreased from 63±17 to 60±17 ml/min/1.73m^2 after 24 weeks of lanreotide (-4.0%;p=0.01;Figure3). This finding was confirmed by changes observed in 24-hours creatinine clearance, which decreased from 79±24 to 74±23 ml/min (-5.6%;p=0.002). Figure 3 illustrated that eGFR primarily declined between baseline and 4 weeks after start of therapy (-3.5%;p=0.004) and remained stable thereafter.

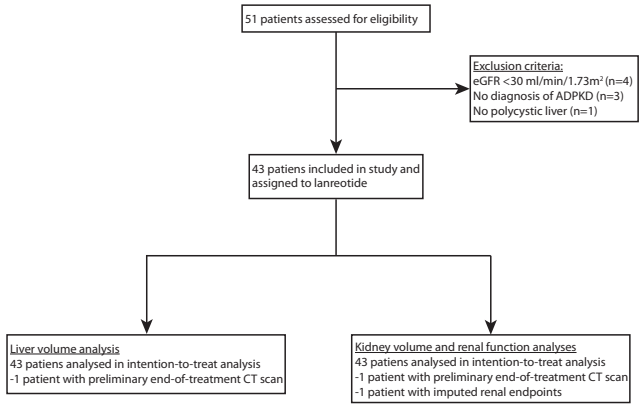

Figure 1: Trial profile. eGFR, estimated glomerular filtration rate; ADPKD, autosomal dominant polycystic kidney disease.

Furthermore, this initial decline in eGFR was associated with a small, although not significant, increase in mean arterial pressure (MAP). We repeated these analyses using the CKD-EPI equation instead of the MDRD equation, as the CKD-EPI equation might estimate renal function more accurately than the MDRD equation. Both analyses gave similar results.

We measured the eGFR in 40 patients after a median follow-up duration of 4.5 months (IQR 3-7 months) after stopping lanreotide. Mean eGFR significantly decreased from 60±17 ml/min/1.73m^2 to 57±17 ml/min/1.73m^2 (-3.4%;p = 0.03; Figure 4). Decline in

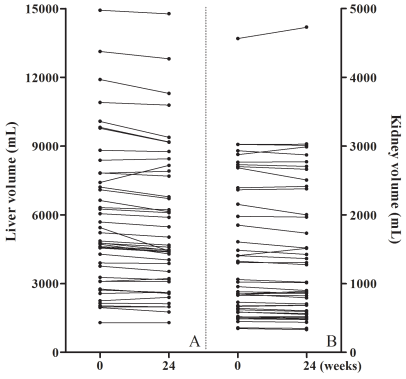

Figure 2: Individual changes in total liver and kidney volumes during therapy. Total liver (A) and kidney (B) volumes in each individual patient (n = 43) at baseline (0 weeks) and after 24 weeks of lanreotide treatment.

eGFR on lanreotide therapy and after stopping was similar, with a reduction of 0.6%/month and 0.8%/month respectively. The decline in eGFR between 4 and 24 weeks of treatment was numerically smaller than after stopping lanreotide (0.0%/month versus -0.8%/month), although this difference was not statistically significant (p = 0.23).

Blood pressure lowering drugs

We started blood pressure lowering drugs in five patients after baseline (Angiotensin-converting-enzyme inhibitor (n=3), diuretics (n=2)), and altered dose of diuretics in two other patients. Since changes in blood pressure affect glomerular filtration, the analyses were also performed after excluding these 7 patients. Again, eGFR initially decreased with -3.6% after 4 weeks of treatment (p=0.008), and was stable between 4 and 24 weeks

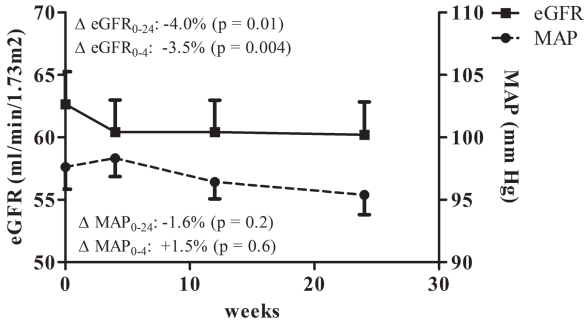

Figure 3: Changes in eGFR and mean arterial pressure during therapy. eGFR, calculated with the MDRD equation, and mean arterial pressure (MAP) at baseline and after 4, 12 and 24 weeks of lanreotide therapy in 43 ADPKD patients evaluated for renal outcomes. Blood pressure data was available for 42 ADPKD patients. eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure. Data is mean with standard error. NOTE: both Y-axis do not intersect at 0 with the X-axis.

of therapy (supplementary Figure2). MAP also increased during these first 4 weeks of therapy, although not significantly (+2.0%;p=0.4). By contrast, the initial decrease in eGFR in the 7 patients who started or changed their blood pressure medication continued after 4 weeks (-10.0%;p=0.008; supplementary Figure3). In parallel, MAP significantly decreased during the same observation period (-8.8%;p=0.03).

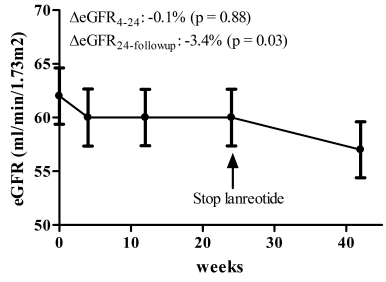

Figure 4: Changes in eGFR during and after stopping lanreotide therapy. eGFR, calculated with the MDRD equation, at baseline, 4, 12 and 24 weeks on lanreotide and after a median of 18 weeks off lanreotide in 40 ADPKD patients evaluated for renal outcomes after stopping lanreotide. eGFR, estimated glomerular filtration rate. Data is mean with standard error. NOTE: the Y-axis does not intersect at 0 with the X-axis.

Gastrointestinal symptoms and Health-related quality of life

We assessed GI symptoms through a specified GI questionnaire. Lanreotide therapy significantly lowered early satiety from 86% to 61% (p=0.003), abdominal distension from 74% to 35% (p<0.001) and shortness of breath from 72% to 51% (p=0.01;Supplementary Table1).

Next, we determined the health status of participating patients through the EQ-5D questionnaire. Treatment with lanreotide had no effect on any of the five dimensions of the EQ-5D or on health state (Supplementary Table2).

Safety endpoints

Adverse events

Four patients receiving lanreotide were hospitalized during the trial. One female patient had urinary tract infection at baseline and developed pyelonephritis with right kidney pyelum obstruction three days after the first lanreotide injection. She was adequately treated with intravenous antibiotics and a double-J ureteral stent. Two other female patients, both with a history of cyst infections, were hospitalized eight and ten weeks after start of lanreotide because of suspicion of liver or kidney cyst infection, respectively. Both patients recovered fully after a course of antibiotics. Finally, one patient was hospitalized with a hepatic cyst bleeding eight weeks after baseline, which was adequately treated with analgesics (Supplementary Table3).

No patient withdrew because of side effects of lanreotide, needed dose reduction or missed a dose. Most common side-effects were diarrhea, loose stools and abdominal cramps which occurred mainly after the first injection and were self-limiting (Supplementary Table3). Seven patients developed mild steatorrhea during the trial, although not confirmed by fecal fat excretion, which was successfully treated with pancreatic enzymes in three participants. No patient developed symptomatic cholelithiasis. One patient with a history of cyst infection developed mild fever, abdominal pain, coughing and malaise 20 weeks after start of lanreotide, and was successfully treated with oral antibiotics for suspicion of hepatic cyst infection at our outpatient clinic.

Laboratory outcomes
Laboratory results showed no clinically relevant or statistically significant changes throughout the treatment period, except for blood glucose levels which moderately but significantly increased from 93.7 to 100.9 mg/dL ($p<0.001$;Supplementary Table4). Elevated glucose levels returned to normal after cessation of lanreotide in all patients. One patient was treated for hyperglycemia which occurred after concomitant use of corticosteroids. Plasma glucose levels returned to normal after ending corticosteroid treatment, and blood glucose lowering therapy was stopped.

Discussion

Our key finding is that 24 weeks of lanreotide therapy significantly reduces liver and kidney volumes in ADPKD patients and that treatment was associated with less postprandial fullness, shortness of breath and abdominal distension. eGFR decreases in the first 4 weeks after start, with a subsequent stabilization on therapy but a further decline after stopping lanreotide.

The observed decrease of 187 ml (-3.1%) in TLV is consistent with previous results. One trial evaluated 6 months of 120 mg lanreotide in 54 patients with polycystic liver disease and found a decrease of -2.9% in TLV.[14] A second trial saw that a 6-month course of long-acting octreotide (40 mg) reduced TLV by -4.5% in 12 ADPKD patients, although these patients had mild polycystic liver disease (mean liver volume 1608 ml).[11] How do these values compare to the natural course of TLV? A recent pooled analysis that included the individual data of all placebo arms from RCTs found that TLV remained stable in ADPKD over the course of 6-12 months.[16] Our results suggest that lanreotide changes the natural course of TLV progression in ADPKD, and that this effect seems unaffected by mild to moderate renal dysfunction (>30 ml/min/1.73m^2). Whether lanreotide therapy is effective in patients with end-stage renal disease remains to be investigated.
Growth of renal volume is much more unrelenting than that of the liver. It is estimated that polycystic kidneys grow by 5.3% annually.[23] This contrasts with results from this trial where lanreotide decreases TKV by 17 ml (-1.7%). These results parallels that of a subgroup analysis from a recent lanreotide trial.[14] By contrast, a cross-over study that evaluated 6 months of octreotide in 12 ADPKD patients found that TKV increased while on therapy, although less than with placebo (+71 ml versus +162 ml).[13] Similar findings were observed in the ALADIN trial, which showed an increase of 46 ml in TKV after 1 year of octreotide therapy in ADPKD patients.[15] This discrepancy could be explained by differences in efficacy between lanreotide and octreotide. Another explanation is that patients included in the octreotide studies had more progressive disease compared to our patients, which is supported by the higher baseline TKV in the cross-over study (2551 ml) and ALADIN (1557 ml) trial compared to the 1023 ml in this trial.
We showed that eGFR significantly decreased after 24 weeks of lanreotide. Of note, there was an initial reduction in eGFR in the first four weeks after baseline and a stabilization thereafter. Several mechanisms may contribute to this initial decline. First, starting antihypertensives in a subset of patients may have contributed to the decline in renal function. However, excluding these patients gave similar results. Second, the decrease in eGFR in the first weeks following the first lanreotide injection suggest causal inference. Indeed, somatostatin acutely decreases GFR in healthy subjects and patients with liver

cirrhosis, probably by renal vasoconstriction.[24-26] The (small) increase in MAP after 4 weeks of treatment also suggests a vasocontrictive effect. It is possible that this acute effect is maintained, causing the decrease in eGFR. Finally, the progression of chronic renal dysfunction in ADPKD decreases eGFR, which adds to a possible vasoconstricting effect of the drug. Our results show that the administration of lanreotide at a dose of 120 mg may cause a significant and irreversible reduction in eGFR, and physicians should be aware of this when starting treatment in ADPKD patients.

We found that eGFR stabilizes beyond 4 weeks of therapy and that eGFR significantly decreases again after stopping lanreotide. This may suggest a renoprotective effect of lanreotide, although a rebound effect or sudden onset of progression of renal disease cannot be excluded. Our hypothesis is supported by the findings from the ALADIN trial, which compared 3 years of long-acting octreotide to placebo in 79 ADPKD patients with preserved or mildly impaired renal function.[15] Both groups showed decreases in measured GFR after 1 year of treatment. Beyond that year, renal function trajectories began to diverge, showing a declining trend in placebo but not for octreotide. These findings suggest that somatostatin analogues may stabilize renal function in ADPKD, although this must be confirmed by future trials that are controlled and adequately powered. Indeed, the DIPAK trial (NCT01616927) is currently evaluating effect of 3 years of lanreotide in 300 ADPKD patients on renal function and includes liver and kidney volume as secondary outcomes.[27]

Lanreotide therapy ameliorated postprandial fullness, shortness of breath and abdominal distension in these patients, but this did not translate in a beneficial effect on health-related quality of life in the short-term. As ADPKD is a chronic disorder, longer follow-up periods and more sensitive questionnaires are probably necessary to properly investigate effects of somatostatin analogues on symptoms and health-related quality of life, preferably in a blinded setting.

Consistent with previous studies, diarrhoea and abdominal cramps were most common side-effects of lanreotide therapy.[14, 28] All hyperglycaemias were reversible and there was no symptomatic cholelithiasis in our study. However, a previous study demonstrated increased prevalence of gallstones in patients with acromegaly who were treated up to 18 years, indicating the potential risks of prolonging therapy.[29] Three patients were suspected of hepatic or renal cyst infection during our study. Even though diagnosis was not confirmed by ^{18}FDG-PET/CT or cyst aspiration and a comparative control arm was lacking, this number seems high as the incidence of cyst infection in ADPKD is estimated at one per 100 patients per year.[30] However, all three patients had an history of cyst infections, which may have increased the risk for new episodes of cyst infections. At any rate, renal dysfunction did not seem to increase side-effects in our trial patients when compared to previous studies, although this must be confirmed in the DIPAK1 trial.

In our opinion, ADPKD patients with highly symptomatic polycystic liver disease ineligible for surgical therapies are good candidates for lanreotide therapy. Our results only apply for a treatment period of 6 months. However, two extension trials showed that prolonging somatostatin analogue therapy resulted in maintenance of the effect up to 2 years in mixed populations of patients with polycystic liver disease.[28, 31] Discontinuation resulted in immediate recurrence of liver growth, indicating that continuous treatment will be necessary to maintain the beneficial effect. However, given the potential risks for long-term treatment, including diabetes and symptomatic cholelithiasis, the use of lanreotide

in ADPKD should be reserved for centres who are familiar with guidelines of prescribing these drugs and have the facilities to perform liver volumetry.
The main strength of this trial is that it showed a clinically relevant decrease in polycystic liver volume in symptomatic ADPKD patients treated with lanreotide. The choice for an observational design guaranteed that a possible effective therapy was not withheld from these symptomatic patients. Although this design precludes direct comparison with untreated ADPKD patients, it increases external validity of our findings. As such they are directly applicable to clinical practice in real life.
There are several limitations to our study worth addressing. First, all included ADPKD patients had a symptomatic polycystic liver, which makes extrapolation of findings to the general ADPKD population difficult. We had a low number of male patients in our study, which reflects the gender imbalance observed in polycystic liver disease. It is unknown whether these results also apply to men with polycystic liver disease. Second, we used prediction formulas to estimate GFR, which may be less reliable than measured GFR. Finally, as we seek polycystic liver targeting, ADPKD patients with only mildly enlarged polycystic kidneys and preserved renal function were not excluded. It is therefore possible that a proportion of patients has PKD2, which has better prognosis that PKD1.[32] Larger controlled trials, including an upper limit of renal function and a longer follow-up period, are needed to determine to properly evaluate the renoprotective effects of lanreotide in ADPKD.
In conclusion, lanreotide reduced polycystic liver and kidney volumes and decreased gastrointestinal symptoms in ADPKD patients. Furthermore, eGFR acutely decreased in these patients, but stabilized after continuation of lanreotide therapy.

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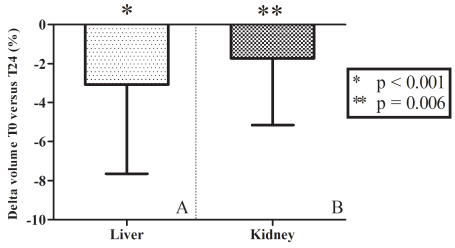
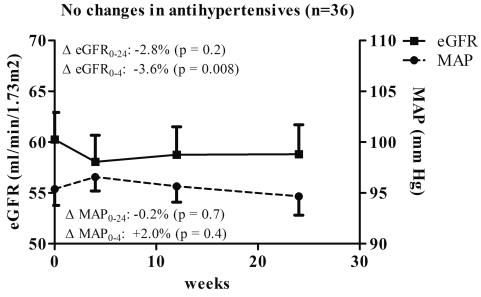
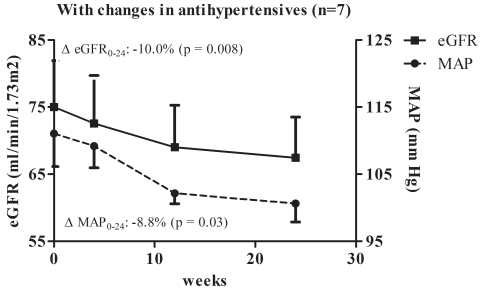
Supplementary files



Supplementary Figure 1: Percent changes in total liver and kidney volumes. Percent change in total liver volume (A) and total kidney volume (B) from baseline after 24 weeks of lanreotide therapy. Data is mean ± standard deviation.



Supplementary Figure 2: Changes in eGFR and mean arterial pressure during therapy in patients without changes in antihypertensives. eGFR, calculated with the MDRD equation, and mean arterial pressure (MAP) at baseline and after 4, 12 and 24 weeks of lanreotide therapy in 36 ADPKD patients evaluated for renal outcomes without changes in antihypertensives. Blood pressure data was available for 35 ADPKD patients. eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure. Data is mean with standard error. NOTE: both Y-axis do not intersect at 0 with the X-axis.



Supplementary Figure 3: Changes in eGFR and mean arterial pressure during therapy in patients with changes in antihypertensives.eGFR, calculated with the MDRD equation, and mean arterial pressure (MAP) at baseline and after 4, 12 and 24 weeks of lanreotide therapy in 7 ADPKD patients evaluated for renal outcomes with changes in antihypertensives. Blood pressure data was available for all 7 patients. eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure. Data is mean with standard error. NOTE: both Y-axis do not intersect at 0 with the X-axis.

Supplementary Table 1: Results of the gastrointestinal symptoms questionnaire

	Lanreotide	
	T0 n/N (%)[a]	**T24 n/N (%)[a]**
Abdominal pain		
In general	16/43 (37%)	14/43 (33%)
Postprandial	11/40 (28%)	11/40 (28%)
Fasting	8/43 (19%)	4/43 (9%)
Unrelated to defecation	7/43 (16%)	6/43 (14%)
Epigastric		
In general	27/43 (63%)	19/43 (44%)
During daytime	23/43 (54%)	17/43 (40%)
At night/asleep	20/43 (47%)	12/43 (28%)
Heartburn	10/43 (23%)	4/43 (9%)
Regurgitation	10/43 (23%)	5/43 (12%)
Nausea	10/43 (23%)	12/43 (28%)
Vomiting	4/43 (9%)	2/43 (5%)
Loss of appetite	14/43 (33%)	16/43 (37%)
Early satiety	37/43 (86%)	26/43 (61%)*
Shortness of breath	31/43 (72%)	22/43 (51%)**
Abdominal distension	32/43 (74%)	15/43 (35%)***
Involuntary weight loss	3/43 (7%)	6/43 (14%)
VAS score[b]	22 (7 to 51)	20 (8 to 31)

* Compared to T0 (p = 0.003). ** Compared to T0 (p = 0.01). *** Compared to T0 (p< 0.001). Abdominal symptom severity ≥ 2 on a 7-point adjectival scale ranging from 0 to 6. VAS, visual analogue scale; scored on a range of 0-100 (0, no pain; 100, worst pain). [a]Denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. [b]Data are median (interquartile range).

Supplementary Table 2: Results of the EuroQol-5D questionnaire

	Lanreotide	
	T0 n/N (%)[a]	**T24 n/N (%)[a]**
Mobility	10/43 (23%)	8/43 (19%)
Self-care	3/43 (7%)	4/43 (9%)
Usual activities	25/43 (58%)	22/43 (51%)
Pain/discomfort	26/43 (61%)	28/43 (65%)
Anxiety/depression	10/43 (23%)	9/43 (21%)
Health state (EQ-VAS)[b]	70 (65 to 80)	71 (68 to 80)

EQ-5D severity ≥ 2 on a 3-point scale (1 = no limitations, 2 = some limitations, 3 = severe limitations). EQ-VAS, EuroQol visual analogue scale; scored on a range of 0-100 (0, worst imaginable health state; 100, best imaginable health state). a Denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. b Data are median (interquartile range).

Supplementary Table 3: Adverse events

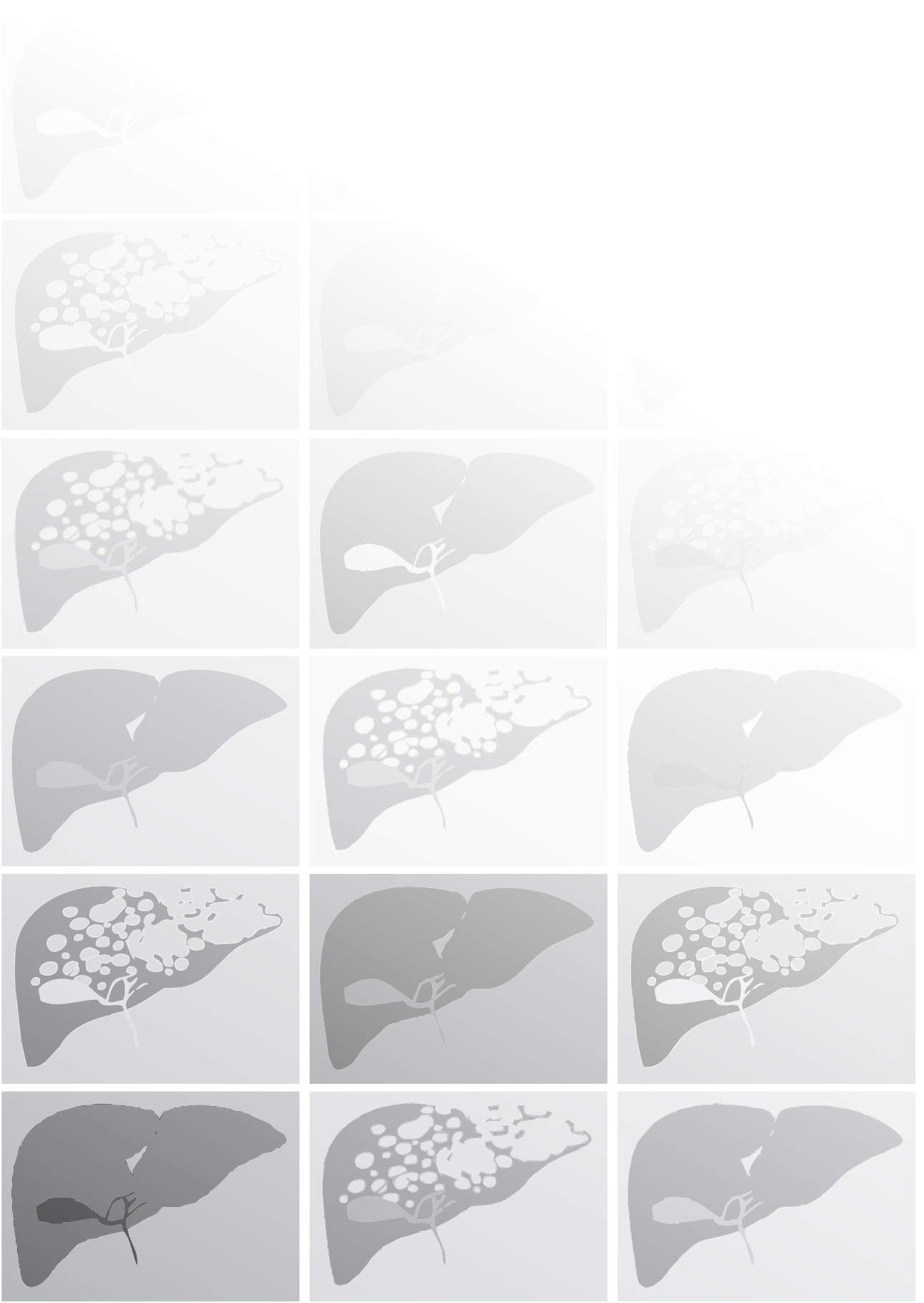
Adverse event	Lanreotide n/N (%)[a]
Diarrhea/Loose stools	35/43 (81%)
Abdominal cramps	34/43 (79%)
Nodule at injection site	17/43 (40%)
Nausea	13/43 (30%)
Flatulence, bloating and gas	8/43 (19%)
Steatorrhea	7/43 (16%)
Constipation	6/43 (14%)
Suspected cyst infection (liver/kidney)[b]	3/43 (7%)
Haemorrhagic liver cyst[c]	1/43 (2%)
Pyelonephritis with right kidney pyelum obstruction[c]	1/43 (2%)

[a] Denominator is total of patients in treatment arm. [b] Two patients were hospitalized. [c] Patient was hospitalized

Supplementary Table 4: Main laboratory parameters at start and end of lanreotide therapy

	T0	T24
Sodium (mmol/L)	139.1 ± 1.9	139.4 ± 1.5
Potassium (mmol/L)	3.9 ± 0.3	3.9 ± 0.7
Calcium (mg/dL)	9.6 ± 0.4	9.6 ± 0.4
Phosphate (mmol/L)	1.0 ± 0.1	1.1 ± 0.2
Bilirubin (mg/dL)	0.7 ± 0.3	0.6 ± 0.2
Serum gamma-glutamyl transferase (U/L)	101 ± 92	107 ± 113
Serum alkaline phosphatase (U/L)	97 ± 80	96 ± 70
Serum albumin (g/L)	39.0 ± 3.4	40.1 ± 3.0
Fasting plasma glucose (mg/dL)	93.6 ± 10.8	100.8 ± 10.8*

Data are reported as mean ± SD.* $p < 0.001$



Chapter 4

Young Women with Polycystic Liver Disease Respond Best to Somatostatin Analogues: a Pooled Analysis of Individual Patient Data

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Abstract

Background & Aims
Clinical trials have shown that in patients with polycystic liver disease (PLD), short-term treatment with somatostatin analogues (SAs) reduces liver volumes by 4.5%−5.9%, compared with placebo. However, the effects of SA theYoung rapy vary among individuals. We collected data from individual patients with PLD to identify subgroups that benefit most from SA therapy.

Methods
We analyzed data from 107 patients with PLD from 3 randomized placebo-controlled trials (67 received SAs, 52 received placebo). We used multiple linear regression analysis to determine the effects of SAs based on patients' age, sex, baseline liver volume, and diagnosis (autosomal dominant polycystic liver disease or kidney disease). The primary outcome was change in liver volume after 6−12 months of treatment.

Results
The effects of SA therapy did not differ significantly among patients with different diagnoses or baseline liver volumes; the overall difference in liver volume between groups receiving SAs therapy vs placebo was 5.3% (P<.001). Among subjects given placebo, young women (48 years old or younger) had the greatest increase in polycystic liver volume (4.8%; 95% confidence interval, 2.2%−7.4%), and mean liver volumes did not increase in older women and men. Women 48 years old or younger had a greater response to therapy (a reduction in liver volume of 8.0%, compared with placebo; P<.001) than older women (a reduction in liver volume of 4.1%, compared with placebo; P=.022).

Conclusions
Based on a pooled analysis of data from individual patients with PLD, treatment with somatostatin analogues is equally effective for patients with autosomal dominant polycystic kidney disease or polycystic liver disease; efficacy does not depend on size of the polycystic liver. Young female patients appear to have the greatest benefit from 6−12 months of SA therapy, which might avert the progressive course of the disease in this specific group.

Introduction

Polycystic liver disease (PLD) is characterized by the progressive formation of multiple fluid-filled cysts throughout the liver, requiring liver transplantation in severe cases.[1, 2] Polycystic livers are the primary presentation in isolated autosomal dominant polycystic liver disease (PCLD), and can manifest as an extrarenal manifestation in autosomal dominant polycystic kidney disease (ADPKD).[3-6] Current available treatment options are mainly surgical and aim at reducing liver volume to ameliorate mechanical symptoms.[7-9] Although these surgical procedures are effective in selected patients, the morbidity rate and their inability to alter the natural course of this disease highlights a clear need for new therapeutic options.

Somatostatin analogues (SAs), such as lanreotide, octreotide and pasireotide, are thought to decrease polycystic liver volume by curtailing cyclic adenosine monophosphate production in hepatic cysts.[10, 11] After a randomized, placebo-controlled, clinical trial (RCT) showing that 6-month long-acting octreotide safely slowed renal volume expansion in ADPKD patients, 3 RCTs demonstrated that the efficacy of long-acting lanreotide or octreotide therapy reversed liver volume growth in PLD patients. [12-15] All trials demonstrated similar responses, with treatment effects of -4.5% to -5.9% in liver volumes when compared with placebo.[16]

However, the treatment effect of SAs in these RCTs varied greatly amongst individual patients, ranging from gains of 300 mL to losses of 1500 mL in liver volume. In addition, results from 2 trials suggested those with larger polycystic livers had greater reductions in liver volume than those with smaller volumes.[13, 14] Risk factors for liver cyst growth are age and female sex, which suggest that these may also impact treatment response to SAs.[17, 18] Finally, one trial reported similar effects of SA therapy in ADPKD and PCLD patients, but this trial lacked power to make final conclusions.[14] Collectively, these findings suggest that treatment responsiveness can be increased in specific subgroups of PLD patients.

Unfortunately, the relatively small number of patients and the specific patient characteristics has precluded any meaningful subgroup analyses within each of these individual RCT. Study level meta-analyses are adequate when estimating a single pooled treatment effect, but are limited in explaining heterogeneity, and do not relate effects of therapy to the single patient. To overcome these limitations and increase statistical power, we performed an individual patient data (IPD) pooled analysis using data from all available placebo-controlled randomized trials and investigated whether the efficacy of SAs is affected by patient factors. Therefore, the aim of the current IPD pooled analysis was to estimate the effect of SAs on polycystic liver volume in PLD subgroups based on underlying diagnosis, sex, age and liver size, to identify patients that respond best to therapy.

Materials and Methods

Literature search
We performed a systematic literature search in the following electronic databases: Pubmed (Medline), Cochrane Controlled Trials Register (CENTRAL), clinical trials.gov, and Web of Science from January 2000 until July 2012. The keywords 'polycystic liver, ADPLD, PCLD or ADPKD' and 'somatostatin, SA, lanreotide, Somatuline®, octreotide, Sandostatine® or pasireotide' and 'placebo' were combined.

Study selection
We included all studies that were randomized, published as full articles or as an abstract, compared the effect of SAs to placebo in adult PCLD or ADPKD patients with a polycystic liver, and reported change in polycystic liver volume as the primary end point. Searches were limited to English, Dutch or German language. Only trials for which we obtained the actual data were included in the analysis. Authors were contacted for additional information in case the methodological quality of a trial was not adequately described in the original article. An additional search was performed using the references of all included trials to retrieve eligible studies possibly missed by our systematic literature search.

Data abstraction
We sent an electronic form containing the data fields to be completed for individual patients to all principal investigators of the trials. Two authors (Tom J. G. Gevers and Joanna IntHout) who had not participated in any of the included RCTs pooled and analyzed all patient data. Subsequently, they checked databases for completeness and internal consistency and made corrections through correspondence with the investigators. The risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[19] The following domains were included for assessment of risk of bias: sequence generation, allocation concealment, blinding (masking) of participants, personnel and outcome assessors, description of the completeness of outcome data for each main outcome, assessment of selective reporting, and other sources of bias specific to the study. Authors were contacted for additional information in case the methodological quality of a trial was not adequately described in the original manuscript.

Outcomes
The primary outcome was change in liver volume as calculated by computed tomography (CT) or magnetic resonance imaging volumetry. The methods of volumetry are presented in detail elsewhere.[12-14, 20, 21] As liver volumes were measured at different follow-up time points, we aggregated the data at 6 months and 12 months of follow-up. Secondary outcomes were safety, tolerability, and fasting plasma glucose levels, as glucose intolerance is a common side-effect of SA therapy. Patient subgroups included in the IPD pooled analysis were underlying diagnosis (ADPKD or PCLD), sex, age, and baseline liver volume. ADPKD was diagnosed in cases where >5 kidney cysts in either one or both kidneys were visible on CT; otherwise patients were diagnosed with PCLD. The age of the patient was assessed at baseline CT or magnetic resonance imaging.

Statistical analysis

The IPD pooled analysis was conducted according to the intention-to-treat principle as described in the original articles.[12-14] As liver volumes have a skewed distribution, we first calculated the logarithms of liver volumes and then carried out the analyses. The treatment effect estimates were backwards transformed and the results were presented as mean percentage differences between SA and placebo, with 95% confidence intervals (CI). In the pooled analysis, we estimated the overall treatment effect of SAs on liver volume, using linear regression analysis with independent variables treatment group (SA or placebo); the logarithm of baseline liver volume; and patient characteristics of sex, age, and underlying diagnosis (APDKD/PCLD). We included the variable study as a fixed effect to take into account the heterogeneity among the different studies, which also included adjustment for differences in length of follow-up (6 vs 12 months). Because one of the trials had a cross-over design, we also included the individual patient as a random factor. For the primary objective, we evaluated the effect of SAs in subgroups by calculating interactions between treatment group (SA or placebo) and possible effect modifiers (diagnosis, sex, age, and logarithm of baseline liver volume). For this purpose, we added each interaction term (treatment group x potential effect modifier) separately to the main model. As multiple factors can affect growth of liver cysts, patients with more than one predisposing factor might have more severe disease and hence have more substantial benefits from SA therapy. Therefore, we subsequently investigated all possible interaction models, with varying combinations of interaction terms (all subsets of variables selection). To assess whether there was difference in fasting plasma glucose levels between treatment group (SA or placebo), we performed an analysis of covariance with post-treatment glucose levels as the dependent variable and baseline glucose levels, treatment group and study as independent variables.

All statistical analyses were performed with SPSS statistical software package version 18.0 (SPSS Inc., Chicago, IL) by Tom J. G. Gevers and Joanna IntHout and without the use of an external data coordinating center. All P values calculated were 2-tailed, and the level of significance was set at $\alpha = .05$.

Role of Funding Source

This study was not supported by any company or grants. The costs were borne by the authors' institutions.

Results

Our search strategy retrieved three RCTs that compared the effect of SA therapy on liver volume with placebo in PLD patients (Supplementary Figure 1). All 3 studies compared long-acting octreotide (Sandostatin LAR®, Novartis Pharma, Basel Switzerland) or lanreotide (Somatuline Autogel®, Ipsen, Boulogne Billancourt, France) with placebo in PLD patients, and each principal investigator agreed to provide individual patient data.[12-14] The first trial evaluated 6 months of lanreotide in 54 patients with PLD.[14] The second trial investigated a 12 month regime of octreotide in 42 PLD patients.[13] Both trials included a mixture of PCLD and ADPKD patients. The third study was a post-hoc analysis performed on a cross-over trial, in which 12 ADPKD patients received both SA and placebo for 6 months.[12] The general characteristics of the 3 trials included in the pooled analysis are

reported in Table 1. Concerning the methodological quality of the RCTs included in this trial, none of the included trials scored a high risk of bias on study or outcome level (Figure 1). In summary, the included trials were conducted in a double-blind fashion used a computer to generate the allocation sequence and reported adequate methods of treatment allocation (pharmacy controlled or central randomization). In addition, radiologists evaluating the primary outcome (liver volume) were blinded to treatment allocation and timing of the scan in all trials.

Baseline characteristics

One female patient, who was randomly assigned to placebo, withdrew after 14 weeks because she was diagnosed with breast carcinoma and was excluded from analysis in the original study.[14] Because this patient did not receive a CT-scan after withdrawal, she was also not included in our analysis.

This resulted in a study population of 107 patients, including 12 patients of the cross-over trial that were measured twice. On average, women were 10 years younger compared with men (43.4 years vs 53.3 years at baseline), and the age of PCLD and ADPKD patients was similar (47.2 years vs 49.6 years). Table 2 shows the characteristics of the participants in each trial; more baseline characteristics are presented in the original articles.[12-14] Patients in the cross-over trial[12] were more often male and had lower liver volumes

Table 1: Design characteristics of the 3 RCTs on SA vs placebo in patients with polycystic liver disease

First author	Design	Trial duration, months	SA	Population	Inclusion criteria	End points
Van Keimpema 2009[14]	RCT (1:1)	6	Lanreotide 120 mg every 4 wks	54 ADPKD/PCLD (27 drug, 27 placebo)	Older than 18 y; > 20 liver cysts	TLV[a], TKV[a], SF36, safety
Hogan, 2010[13]	RCT (2:1)	12	Octreotide 40 mg every 4 wks	42 ADPKD/PCLD (28 drug, 14 placebo)	Older than 18 y; liver volume > 4000 ml or symptomatic liver disease and no candidate for surgery	TLV[b], TKV[b], mGFR, SF36, safety
Caroli, 2010[12]	Randomized, cross-over[c]	6	Octreotide 40 mg every 4 wks	12 ADPKD (both drug and placebo)	Older than 18 y; serum creatinine <265 μmol/L, but >106 μmol/L (men) or >88 μmol/L (women)	TLV[a], TKV[a], mGFR, safety

mGFR, measured glomerular filtration rate; SF36, short form (36) Health Survey; TKV, total kidney volume; TLV, total liver volume. [a]Measured by computerized tomography. [b]Measured by Magnetic Resonance Imaging. [c]Secondary post-hoc analysis performed on data of this cross-over study.

than participants in the other 2 trials.[13, 14] In addition, no PCLD patients were included in the cross-over trial.[12] There were no significant differences in baseline characteristics between placebo and SA-treated patients (Table 2).

Pooled analysis

A total of 119 treatment periods, 67 in the group allocated to SA therapy and 52 in the placebo group, were included for analysis of change in liver volumes. No patient died or had a liver transplantation during the treatment periods. The majority of patients receiving an SA (82%) and only 44% of patients on placebo had a decrease of liver volume from baseline (Supplementary Figure 2). Reponses to SA therapy varied from increases of 9.7% to decreases of 17.3% in liver volume compared with baseline, indicating the large variability in treatment responses. After 6-12 months on placebo, the estimated

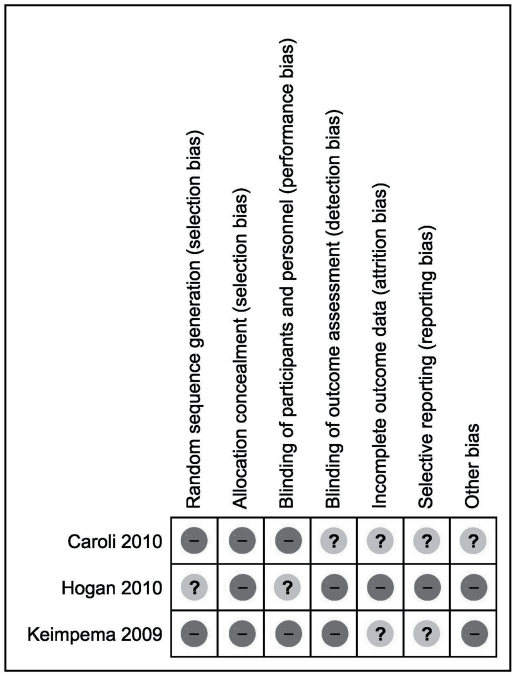

Figure 1: Risk of bias summary: review of authors' judgments about each risk of bias item for each included study. -, low risk of bias; ?, unclear risk of bias; +, high risk of bias.

mean liver volume increased with 1.8% (95% CI: 0.0% to 3.8%) compared with baseline. In contrast, SA treatment resulted in a reduction of 3.6% (95% CI: -5.2% to -2.0%) (Supplementary Figure 3). Together, this resulted in an overall significant treatment effect of -5.3% in liver volume (95% CI -7.2% to -3.4%; P < .001) on SA therapy (Table 3). In order to assess whether we could aggregate data, we performed a sensitivity analysis comparing the effects of SA therapy from the 12-month trial [13] with effects observed in the 6-month trials. [12, 14]. In both placebo and SA arms, we found no significant differences in change of liver volume between 6 and 12 months of follow-up (P = .49 and P = .87).

Diagnosis

The effect of SA therapy was evaluated in PLD subgroups with PCLD and ADPKD as underlying diagnoses. On placebo, mean liver volume increased from baseline in PCLD patients, and it remained stable in ADPKD patients (3.8% vs 0.1%; p = .011) (Figure 2). In both subgroups, the significant treatment effects of SAs on liver volume were similar (-5.6% vs -5.2%; P = .87), indicating that diagnosis did not significantly affect treatment response (Table 3).

Sex

Women on placebo had an average increase of 2.9% in liver volume from baseline, whereas livers did not grow noticeably in male patients on placebo (-0.1%) (Supplementary Figure 4). SA therapy decreased liver volume to a similar extent in female and male patients (-3.6% vs -2.7%) compared with baseline. This resulted in a significant treatment effect of SAs in female patients (-6.4%; P < .001) when compared with placebo, and SA therapy was not significantly effective in men (-2.5%; P = .20), and a nonsignificant trend towards a better response was found in female PLD patients (P = .074) (Table 3).

Table 2: Baseline characteristics of included patients with polycystic liver disease in each trial and each treatment group

	van Keimpema et al, 2009[14]	Hogan et al, 2010[13]	Caroli et al, 2010[12]	**Combined treatment groups**	
	(n = 53)	(n=42)	(n=12)	SA (n=55)[a]	Placebo (n=40)[a]
Age, y, median (range)	48 (32 – 67)	47 (34 – 69)	44 (33 – 57)	47 (32 – 69)	49 (36 – 67)
Sex, n (%)					
Female	46 (87)	36 (86)	3 (25)	47 (85)	35 (88)
Male	7 (13)	6 (14)	9 (75)	8 (15)	5 (12)
Diagnosis, n (%)					
PCLD	22 (42)	8 (19)	0 (0)	19 (35)	11 (27)
ADPKD	31 (58)	34 (81)	12 (100)	39 (65)	29 (73)
Liver volume, mL, median (range)	4681 (1728 – 10,252)	4452 (2234 – 13,148)	1525 (1109 – 2788)	4505 (1728 – 11,766)	4707 (2004 – 13,148)
Weight, kg, median (range)	71 (52 – 95)	72 (50 – 130)	74 (58 – 100)	71 (50 – 130)	72 (53 – 93)
BMI, median (range)	25 (20 – 34)	25 (18 – 41)	25 (21 – 33)	25 (18 – 41)	25 (20 – 33)
Serum bilirubin, µmol/L, median (range)	10 (9 – 32)	9 (5 – 27)	14 (5 – 26)	9 (5 – 32)	10 (5 – 27)
Serum γ-glutamyl transferase, U/L, median (range)	73 (19 – 500)	ND	17 (2 – 51)	85 (19 – 500)[b]	71 (25 – 465)[b]
Serum alkaline phosphatase, U/L, median (range)	127 (36 – 697)	83 (45 – 276)	67 (36 – 89)	91 (36 – 697)	101 (56 – 298)
Serum albumin, g/L, median (range)	4.3 (3.2 – 4.9)	4.3 (3.9 – 4.8)	4.2 (3.9 – 4.9)	4.3 (3.2 – 4.9)	4.3 (3.8 – 4.9)
Serum creatinine, µmol/L, median (range)	71 (53 – 212)	80 (53 – 230)	150 (97 – 301)	80 (53 – 230)	71 (53 – 203)
Serum glucose, mmol/L, median (range)	5.0 (4.0 – 7.5)	5.1 (4.6 – 7.3)	4.9 (4.1 – 6.4)	5.0 (4.2 – 7.5)	5.1 (4.0 – 7.3)
Therapy, n (%)					
SA	27 (51)	28 (67)	12[c] (100)	-	-
Placebo	26 (49)	14 (33)	12[c] (100)	-	-

BMI, Body Mass index; ND, not determined. [a]Patients from the trial of Caroli et al[12] were excluded because these patients received both an SA and placebo. [b]Including data from the trial of Keimpema et al[14] only. [c]Patients in the trial of Caroli et al[12] received both an SA and placebo.

Age

Age did not significantly influence the liver volume-reducing effects of SAs (P = .23) (table 3). Subsequently, we estimated the effect of SAs in age subgroups using the median of 48 years as a cut-off value. Younger patients showed more increase in liver volume on placebo than older patients (2.9% vs 0.5%) (Supplementary Figure 5). In both patients 48 years old and younger and patients older than 48 years old, the effect of SA therapy was significant when compared with placebo (-6.7% and -3.7%; P < .001 and P = .013).

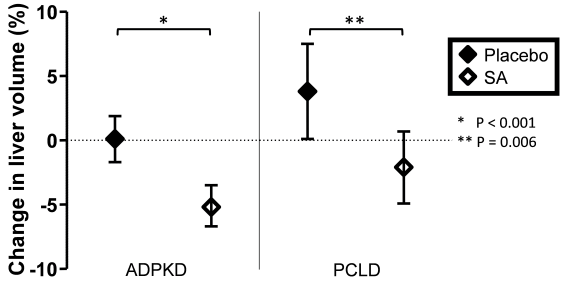

Figure 2: Estimated percent changes (mean ± 95% CI) in liver volumes in ADPKD and PCLD patients treated with somatostatin analogues or placebo for 6-12 months, calculated by multiple linear regression analysis.

Baseline liver volume

We also evaluated the impact of polycystic liver size on treatment effect and observed that liver size did not affect mean response to SA therapy (P = .56) (Table 3). Next, we determined the effect of SA therapy in 2 subgroups of polycystic liver volumes, with low to medium volumes categorized as below the median and high volumes categorized as above the median. In both subgroups, patients had similar increases in liver volume on placebo (1.6% vs 2.4%) and showed significant treatment responses to SA therapy (-4.5% and -6.5%; P = .001 and P < .001).

Table 3: Estimated mean percent changes in liver volumes after 6-12 months (SA compared with placebo), calculated by multiple linear regression analysis.

Patient group	SA vs placebo, % (95% CI)	P value	Effect modifier (P value)
All	-5.3 (-7.2 to -3.4)	<.001	NA
Diagnosis			No (0.87)
ADPKD	-5.2 (-7.5 to -3.0)	<.001	
PCLD	-5.6 (-9.5 to -1.7)	.006	
Sex			Trend (0.074)
Women	-6.4 (-8.5 to -4.2)	<.001	
Men	-2.5 (-6.3 to 1.5)	.20	
Age[a]			No (0.23)
48 y or younger	-6.7 (-9.2 to -4.2)	<.001	
Older than 48 y	-3.7 (-6.5 to -0.8)	.013	
Baseline liver volume[a]			No (0.56)
Low/Medium (≤ 4256 ml)	-4.5 (-7.0 to -1.9)	.001	
High (> 4256 ml[a])	-6.5 (-9.4 to -3.5)	<.001	

NA, not applicable. [a]Age and baseline liver volume groups are defined by the median as the cut-off value

Age-Sex subgroups

Post hoc, we performed an additional subgroup analysis, including patients with more than one predisposing factor, and included a subgroup for sex combined with age, using the median of 48 years as a cut-off value. On placebo, women 48 years old and younger had the largest growth in polycystic liver volume compared with baseline (4.8%), and liver volumes did not grow in women older than 48 years and in men (Figure 3). All subgroups had similar reductions in liver volume after SA therapy when compared with baseline. In both women 48 years old and younger and women older than 48 years, the treatment effects of SA on liver volume were significant (-8.0%; P < .001 and -4.1%; P = .022) when compared with placebo, with the best response in the younger women group (Table 4). In contrast, both men 48 years old and younger and men older than 48 years failed to show a significant treatment effect of SAs (-1.8%; P = .53 and -3.1%; P = .23). Overall, it seems that SA therapy is most beneficial for female PLD patients 48 years old and younger, although treatment interaction did not reach statistical significance (P = .084).

Safety and tolerability

No severe adverse events related to SA therapy were reported in the included RCTs. Although 3 patients receiving an SA were hospitalized during the 1-year study period of one trial, the causes were deemed to be unrelated to the study medication (ie, incarcerated abdominal hernia, abdominal pain and fever responding to antibiotic treatment, and bacteremia associated with nephrolithiasis).[13] In contrast, no patient on placebo was hospitalized. In addition, one patient had pre-existent asymptomatic nonobstructing gallstones, and another had gallbladder sludge. Both findings remained stable on SA therapy.[13] Most common side effects related to SA therapy were gastrointestinal and included diarrhea/loose stools (51%); abdominal cramps (34%); and flatulence, bloating, and gas (30%) (Supplementary Table 1). Ten patients (15%) developed steatorrhea during SA therapy, which resolved in most patients after treatment with pancreatic enzymes. Persistent injection-site swelling was reported in 25% of patients on SAs compared with 2% of patients on placebo. In one trial, doses of SA were reduced in 7 patients, mainly due to gastrointestinal side effects.[13] In contrast, no patients in the placebo group required a dose reduction. Mean fasting plasma glucose levels increased from 5.2 mmol/L (95% CI: 5.1 - 5.4 mmol/L) to 5.6 mmol/L (95% CI: 5.4 - 5.8 mmol/L) in the SA group. In contrast,

Table 4: Outcomes in age-sex subgroups: estimated mean percent changes in liver volumes after 6-12 months, calculated by multiple linear regression analysis

Patient group	SA v s baseline , % change (95% CI)	Placebo v s baseline , % change (95% CI)	SA v s placebo , % change (95% CI)	P-value	Interaction (P value)
Age-Sex[a]					trend (.084)
Women					
48 y or younger	-3.5 (-5.6 to -1.5)	4.8 (2.2 to 7.4)	-8.0 (-10.6 to -5.2)	<.001	
Older than 48 y	-3.5 (-6.0 to -0.9)	0.6 (-2.5 to 3.8)	-4.1 (-7.4 to -0.6)	.022	
Men					
48 y or younger	-3.5 (-7.4 to 0.6)	-1.8 (-6.2 to 2.8)	-1.8 (-7.2 to 4.0)	.53	
Older than 48 y	-2.6 (-5.9 to 0.8)	0.5 (-3.3 to 4.5)	-3.1 (-7.8 to 1.9)	.22	

NA, not applicable. [a]Age groups defined by the median as the cut-off value.

fasting glucose levels remained stable in the placebo group, with an increase from 5.2 mmol/L (95% CI: 5.0 - 5.3 mmol/L) to 5.1 mmol/L (95% CI: 4.9 - 5.3 mmol/L). Although this difference was significantly different between both treatment groups (P = .005), no patient developed diabetes or required antidiabetic therapy.

Discussion

The key finding of our IPD pooled analysis is that underlying diagnosis (ADPKD or PCLD) and liver size had little influence on the significant liver volume-reducing effect of SAs in PLD patients. However, untreated young women (48 years old and younger) in particular have the largest increase in polycystic liver volume (+4.8%) and responded best to SA therapy (-8.0%) when compared with placebo.

We did not find a significant interaction between polycystic liver size at baseline and treatment allocation, suggesting the benefit of SA therapy was similar for all polycystic liver sizes. This seems in contrast to the individual results of 2 trials that were included in our analysis, where both trials observed that larger livers had more volume reduction than smaller livers. [13, 14] However, these trials assessed absolute change in liver volume instead of percent changes and did not include a comparison with a placebo group, which might lead to biased results.

We observed that polycystic livers grow significantly faster in PCLD patients compared with ADPKD patients. One observational study compared the natural course of PLD in 34 ADPKD and 19 PCLD patients and showed that PCLD patients had significant greater number and larger size of liver cysts.[22] The more progressive course in PCLD may be explained by differences in expression of underlying genetic mutations, although there is no experimental evidence supporting this hypothesis.

Based on our analysis, the growth rate of polycystic livers is estimated at 1.8% in 6-12 months. The observed liver growth of 4.8% in young women is a clear departure from the growth rate in older women and men of all ages (0.6% and -0.1%), strongly suggesting a hormonal influence. This hypothesis is supported by previous studies that established multiple pregnancies and exogenous estrogens as risk factors for growth of hepatic cysts.[23, 24] In addition, 1 year of postmenopausal estrogen therapy increased polycystic liver volume 7% in ADPKD women; liver volumes did not change in controls.[25] However, none of the included patients in our study were pregnant or used oral contraceptives, suggesting premenopausal status in women is an independent risk factor for polycystic liver growth. Cholangiocyte proliferation is considered one of the major contributors to hepatic cystogenesis and is significantly increased by estrogens in vitro.[2, 26, 27] Unfortunately, it was not possible to investigate whether the increase in liver growth also aggravated symptoms in these patients, as only one study evaluated change in symptoms.[14]

The effect of SA therapy was most pronounced in women 48 years old or younger. The beneficial response might be caused by averting the progressive course of PLD observed in these patients, thereby suggesting that therapy is more effective in fast-growing polycystic livers. However, the increased liver growth in PCLD patients compared with ADPKD patients did not lead to an increase in treatment effect (-5.6% vs -5.2%), indicating that other factors might be involved. One study showed that the efficacy of octreotide to suppress cyclic adenosine monophosphate accumulation in female rat pituitary cells increased after treatment with 17 β-estradiol.[28] This suggests that estrogens, apart from

increasing cholangiocyte proliferation, might also enhance the ability of SAs to inhibit cyclic adenosine monophospate production in cholangiocytes, and can increase susceptibility to SA therapy in fertile women. To evaluate whether this mechanism is of importance in hepatic cystogenesis, this result must first be reproduced in a cholangiocyte cell line.

As such, our results may lend credence to the concept that short-term SA therapy benefits young female PLD patients in particular. In addition, our results provide extra support for avoidance of other risk factors (ie, exogenous estrogens) for young female PLD and PCLD patients in particular, as these individuals already may have a more progressive disease course. The failure to detect a significant positive effect of SA therapy in male PLD patients is possibly due to the low number of these patients. Therefore, we think it is premature to withhold therapy from this subgroup, especially as there are individual male PLD patients who are responding. If clinicians want to replicate these results in clinical practice, they have to follow the inclusion criteria used in the RCTs and become familiar with the side-effect profile and guidelines for the prescribing these drugs in the context of renal insufficiency. In addition, the findings presented here only apply for a short treatment regimen of 6-12 months. Extension of SA therapy beyond this time period might result in improved, or maintenance of, treatment effects, as 2 recent extensions of 2 of the included RCTs have shown.[29, 30] One extension trial demonstrated that 6 months of lanreotide (120 mg injected monthly) resulted in a 4.0% reduction in liver volume from baseline, which was maintained for the remainding 6 months of therapy.[29] Similarly, another extension trial demonstrated that the effect of octreotide (40 mg injected monthly) was -5.2% in the first 12 months, and that this reduction did not change significantly after another 12 months of therapy (-0.8%, P = .57).[30] Although both extension trials did not include a control group, these findings indicate that SAs curtail polycystic liver growth up to 2 year. In addition, discontinuation resulted in immediate recurrence of liver growth, suggesting that continuous treatment is necessary to maintain this beneficial effect.[29] Given the expense of treatment, it is paramount to establish on-treatment effects that would warrant long-term therapy. As the natural course of PLD varies between PLD patients, it is insufficient to look at a fixed threshold of liver volume reduction alone. Therefore, we suggest determining the (semi-)annual liver growth rate in a PLD patient before initiating SA therapy, which can be compared with the on-treatment effects of SA. If this effect is smaller than a certain threshold, SA therapy should be discontinued. Ideally, this threshold is correlated to a clinical significant effect, for example, symptom resolution. Points of discussion are how to handle patients without a progressive course of PLD or with aggravation of symptoms during therapy.

The current treatment strategy for PLD includes laparoscopic fenestration, partial hepatectomy, and liver transplantation, and is indicated in symptomatic patients.[1, 31, 32] If a patient has several large superficial liver cysts, laparoscopic fenestration is the best therapeutic choice. Partial hepatectomy can be considered if patients have cyst-rich segments with at least one segment spared, and liver transplantation is only indicated in patients with a severely impaired quality of life or untreatable cyst-related complications. Before including SA therapy into the existing treatment strategy, it is important to be familiar with recurrence rates and complications of long-term use of SAs and how they relate to established surgical options. Addressing these questions will provide more insight in which patients will benefit from long-term treatment with SAs or surgery. At this time, SA therapy may be only considered in highly symptomatic patients that are not

eligible for surgical intervention. Future roles for SAs include delaying the need for liver transplantation or combined with surgery to optimize clinical results.
The main strength of our study is that we included the individual patient data of all RCTs that compared SA with placebo in PLD patients. In addition, the wide range in baseline characteristics among included RCTs allowed us to thoroughly investigate the influence of these characteristics on therapeutic response. Although one study was a post-hoc analysis on a cross-over trial[12], none of the included studies had a high risk of bias for one or more key domains. Almost all patients completed the trial with only 1 dropout in the placebo group. A sensitivity analysis using the baseline liver volume of this patient as the end point showed no differences with the original analysis, indicating that exclusion of this patient did not influence our findings.
Study limitations include the 2 types of SA (octreotide and lanreotide) that were investigated in our IPD pooled analysis. To our knowledge, no study has directly compared the efficacy of lanreotide and octreotide in PLD patients. The average effects of SA therapy in all included RCTs were very similar, suggesting that the efficacy of octreotide and lanreotide is comparable in PLD. Several studies in patients with acromegaly reported comparable effects of long-acting lanreotide and octreotide, thereby indicating that that these drugs share pharmacodynamic profiles.[33, 34] One of the included RCT had a cross-over design and did not include a washout period between the 2 arms.[12] However, the observed treatment effect was independent of treatment sequence in this trial, thereby excluding any considerable carry-over effect. The duration of included trials were not similar, as 2 trials evaluated the effect of SA therapy in 6 months[12, 14] and 1 trial had a follow-up of 1 year.[13] We performed a sensitivity analysis that showed no notable differences in effect of placebo and SAs on change in liver volume between 6 and 12 months of follow-up. These findings indicate that the 6-month and 12-month data could be aggregated in our IPD pooled analysis. In addition, to control for the possible differences in methodological designs between the included RCTs, including differences in follow-up time, we included study as a variable in our IPD pooled analysis.

In conclusion, we show that in patients with PLD, SA therapy is equally effective in ADPKD and PCLD patients; the size of the polycystic liver does not affect the response to SAs; young female patients (48 years old and younger) have the largest growth in liver volume in 6-12 months, and seem to have the most substantial effect of SA therapy. Additional large-scale multicenter studies evaluating the long-term effects of SAs on liver volume and symptom resolution in PLD patients are necessary to substantiate the merits of this therapy.

Acknowledgements

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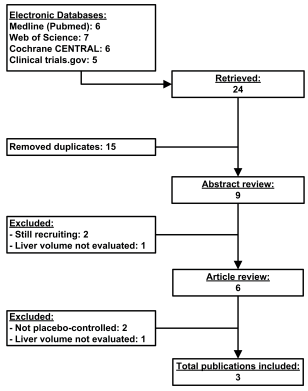
Author names in bold designate shared co-first authorship

Supplementary files

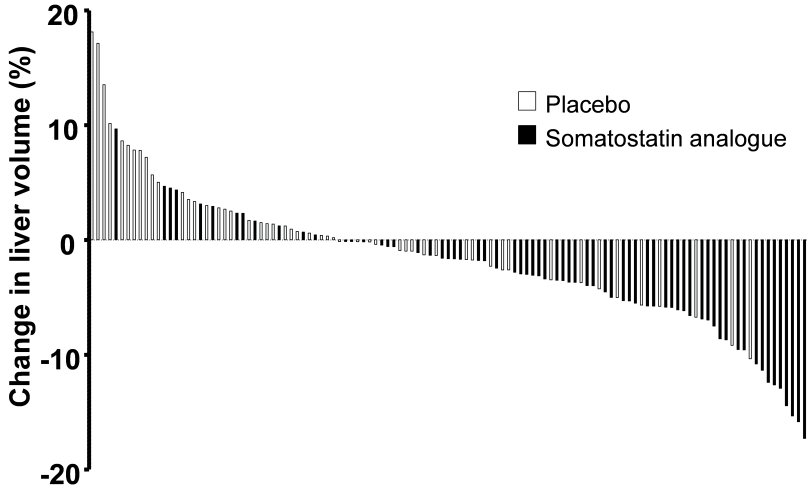
Supplementary table 1: Adverse events

Adverse event	Somatostatin analogue n/N[a] (%)	Placebo n/N[a] (%)
Diarrhea/Loose stools	34/67 (51)	7/52 (13)
Abdominal cramps	23/67 (34)	1/52 (2)
Flatulence, bloating and gas	20/67 (30)	3/52 (6)
Persistent injection site swelling	17/67 (25)	1/52 (2)
Steatorrhea	10/67 (15)	0/52 (0)
Nausea	9/67 (13)	3/52 (6)
Constipation	4/67 (6)	1/52 (2)

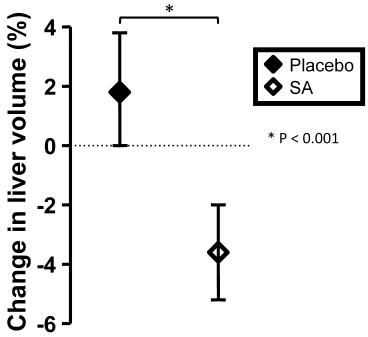
[a]Denominator is total of patients in treatment arm



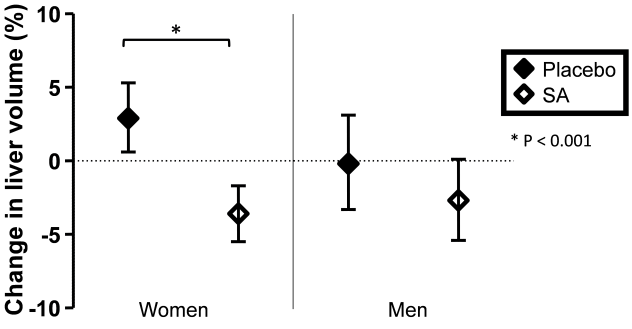
Supplementary Figure 1: Flow diagram of selection articles.



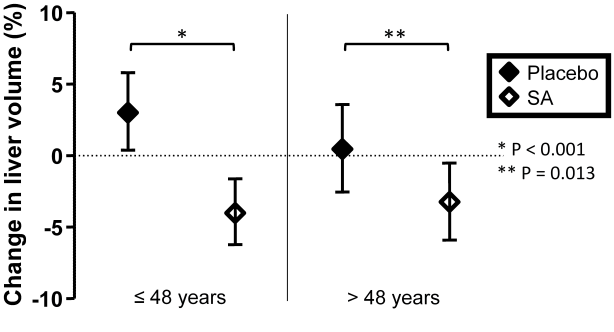
Supplementary Figure 2: Percent changes in liver volume for all treatment periods. Each bar represents 1 treatment period (n=119).



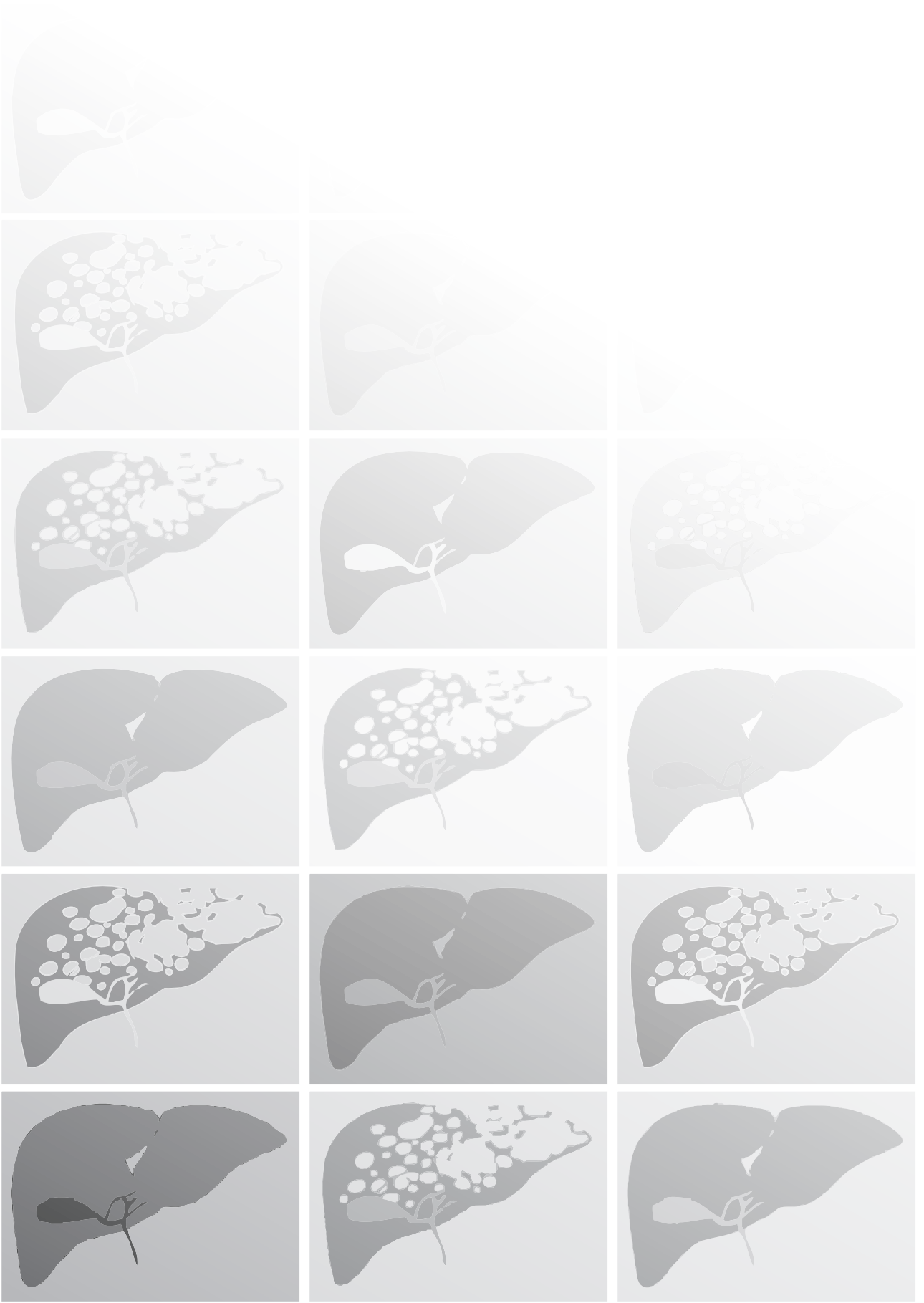
Supplementary Figure 3: Estimated percent changes (mean ± 95% CI) in liver volume in all patients treated with somatostatin analogues or placebo for 6-12 months, calculated by linear multiple regression analysis.



Supplementary Figure 4: Estimated percent changes (mean ± 95% CI) in liver volumes in men and women treated with somatostatin analogues or placebo for 6-12 months, calculated by multiple linear regression analysis.



Supplementary Figure 5: Estimated percent changes (mean ± 95% CI) in liver volumes in age subgroups (median of 48 years as a cut-off value) treated with somatostatin analogues or placebo for 6-12 months, calculated by multiple linear regression analysis.



Chapter 5

Elevated alkaline phosphatase predicts response in polycystic liver disease patients during somatostatin analogue therapy

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Submitted

Abstract

Background&Aims
Somatostatin analogues reduce liver volumes in polycystic liver disease. However, patients show considerable variability in treatment responses, making it difficult to predict response to therapy. Our aim was to identify specific patient, disease or treatment characteristics that predict response in polycystic liver disease during somatostatin analogue therapy.

Methods
We pooled the individual patient data of 4 trials that evaluated long-acting somatostatin analogues (120 mg lanreotide or 40 mg octreotide) for 6 or 12 months in polycystic liver disease patients. We performed uni- and multivariate linear regression analysis with 9 preselected patient, disease and drug variables to identify independent predictors of response, defined as percent change in liver or kidney volume (in ADPKD subgroup). All analyses were adjusted for baseline liver volume and center.

Results
We included 153 polycystic liver disease patients (86% female, mean age 50 years, median liver volume 4974 ml) from 3 international centers, all treated with octreotide (n=70) or lanreotide (n=83). Mean reduction in liver volume was 4.4% (range -31.6% to +9.4%). Multivariate linear regression revealed that elevated baseline alkaline phosphatase was associated with increased liver volume reduction during therapy (-2.7%,95% CI -5.1% to -0.2%,p=0.04), independently of baseline liver volume. Somatostatin analogue type, underlying diagnosis and eGFR did not affect response. In our ADPKD subpopulation (n=100), elevated alkaline phosphatase again predicted liver volume reduction (-3.2%,p=0.03) but did not predict kidney volume reduction (+0.1%, p=0.97).

Conclusion
Elevated alkaline phosphatase is a liver-specific, independent predictor of response in polycystic liver disease during somatostatin analogue therapy.

Introduction

Polycystic liver disease (PLD) is common in patients with autosomal dominant polycystic liver disease (PCLD)[1, 2] and autosomal dominant polycystic kidney disease (ADPKD).[3] The progressive enlargement of the liver causes chronic symptoms and results in reduced quality of life in these patients.[4] Somatostatin analogues (SAs), such as lanreotide and octreotide, are cyclic adenosine monophosphate (cAMP) level inhibitors and decrease polycystic liver volume.[5, 6] Recently, a recent meta-analysis showed that 6-12 months of SAs decreased polycystic liver volume with 5.3% in PLD patients when compared to placebo.[7] This clearly supports the thesis that growth of polycystic liver can be suppressed by SAs.

While the overall majority of PLD patients respond to SAs therapy, there is great interindividual variability which makes it difficult to predict which patients will respond favorably. This can be due to patient related factors as it has been suggested that patients with larger polycystic livers had higher reductions in absolute liver volume in two studies that evaluated lanreotide in PLD.[8, 9] Likewise pharmacokinetic factors such as body weight or renal function may influence pharmacodynamic properties of SA.[10] On the other hand exogenous factors such as different SA types may affect treatment responses. Finally, liver enzymes including alkaline phosphatase (ALP), gamma-glutamyl transferase and bilirubin are elevated in PLD patients and may be associated with disease progression.[11, 12] By identifying specific patient, disease or treatment related characteristics that are associated with response, we can select patients that will have higher success rates on therapy. This will allow for a more individualized therapy preventing unnecessary and ineffective SA therapy. Furthermore, identifying predictors of response will provide more insight in how these factors affect liver volume progression in PLD. Unfortunately, the small number of patients from individual studies precluded the analysis of predictors. We therefore performed a pooled analysis on individual patient data of four trials that evaluated SA therapy in PLD patients to overcome this limitation.

In this study, we investigate which patient, disease and treatment factors are independently associated with response in PLD patients, and explore the relationship between these factors and liver volume progression during SA therapy.

Methods

Population

We included the individual patient data (IPD) coming from 4 trials that described the effect of long-acting SAs (120 mg lanreotide or 40 mg octreotide) for 6 or 12 months in adult PLD patients and had change in liver volume as the primary outcome. We contacted the authors from the following trials for inclusion of data: LOCKCYST trial + extension (NCT00565097/ NCT00771888) [9, 13], Mayo Clinic trial + extension (NCT00426153) [14, 15], ELATE trial (NCT01157858) [16] and RESOLVE trial (NCT01354405) [17]. In the LOCKCYST trial, 54 patients with PLD (ADPKD n=32; PCLD n=22) were randomized to monthly injections of lanreotide 120 mg or placebo for 6 months. Treatment was extended to a total of 12 months in 41 of 54 PLD patients in the LOCKCYST extension study. The Mayo Clinic trial evaluated the effect of long-acting octreotide 40 mg given monthly for a year in 42 patients with ADPKD (n=34) or PCLD (n=8). Patients were randomized 2:1 to octreotide

and placebo respectively. The Mayo Clinic trial also extended SA therapy with 1 year for 41 of the 42 patients, which enabled patients in the placebo arm to be treated. The ELATE trial randomized 44 patients (combined ADPKD and PCLD) to octreotide combined with everolimus or to octreotide monotherapy. Because the difference in liver volume changes was not significant between the two treatment arms ($p = 0.73$), we included patients from both treatment arms. Finally, the RESOLVE trial investigated the effect 6 months of lanreotide in 43 ADPKD patients in an uncontrolled study.
All study protocols of included trials conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee, and all patients who participated in the studies provided written consent.

Data Acquisition
We sent an electronic form containing the data fields to be completed for individual patients to all principal investigators of the trials. The primary author (T.G) pooled all data, checked databases for completeness and internal consistency and made corrections through correspondence with the investigators. We included all PLD patients with ADPKD or PCLD as the underlying disease and received SA therapy for more than 3 months in one of the 4 aforementioned trials. We collected liver and kidney volumes at baseline and end of therapy. We obtained the following candidate predictors at baseline: sex, age, diagnosis, weight, estimated glomerular filtration rate (eGFR), SA type (lanreotide or octreotide), ALP, gamma-glutamyl transferase and bilirubin. In addition, everolimus-cotherapy and length of SA therapy were recorded. In case the patient participated in multiple trials, only the first trial period was included in the analysis.

Outcome definitions
The primary outcome was response defined as change in liver volume at end of therapy compared to baseline. Liver volumes were calculated by CT- or MRI volumetry as described in detail elsewhere.[9, 15, 18] All CT and MRI scans were blinded to patient identity, date of birth and date of scan at time of measurement. As liver volumes were measured at different follow-up time points, we aggregated the data at 6 months and 12 months of follow-up. Secondary outcomes was change in kidney volume at end of therapy compared to baseline. The adjusted Ravine criteria were used to diagnose ADPKD; if patients did not fulfill the criteria, they were diagnosed as PCLD.[19] The patient's age was determined at time of the baseline CT or MRI. We dichotomized weight to $<$ or $\geq$ 75 kg, using the mean as a cut-off. eGFR was assessed by using the 4-variable MDRD formula, and we included eGFR both continuous and dichotomized to $<$ 60 or $\geq$ 60 ml/min/1.73m^2.[20] ALP, gamma-glutamyl transferase and bilirubin were dichotomized to either elevated or normal. Because different cut-offs were used for ALP in laboratories, we compared ALP levels to the upper limits of normal (ULN) and calculated as a ratio. ALP was considered to be elevated if levels at baseline were greater than a ratio of 1 and considered to be normal if the values had a ratio of 1 or less.

Statistical analysis
The IPD pooled analysis was conducted according to the intention-to-treat principle. As liver volumes have a skewed distribution, we first calculated the logarithms of liver volumes and then carried out the analyses. Effect estimates were backwards transformed

and the results were presented as mean percentage differences, with 95% confidence intervals (CI). We performed univariate and multivariate linear regression to determine which variables were associated with the outcome liver volume. Variables with $p < 0.2$ in the univariate analysis were selected for the multivariate analysis. We used backward selection to exclude variables in the multivariate analysis, variables with a p-value of 0.05 retained in the model. We included the variable center as a random effect in all analyses to take into account the heterogeneity among the different centers. In addition, we adjusted for baseline liver volume in all analyses.
In order to check whether we could aggregate the 6 and 12 months treatment data, we added treatment duration (6 vs 12 months) of SA therapy to the final model. Similarly, we performed analysis using everolimus co-therapy as an independent variable to investigate whether everolimus co-therapy was associated with response.
For the secondary outcome change in kidney volume, we performed multivariate linear regression analysis in ADPKD patients. We included all significant predictors from the primary multivariate analysis as independent variables and adjusted for baseline kidney volume.
To determine the probabilities of achieving a good response, defined by different cut-offs in change in liver volume, we performed logistic regression analysis, including good response (yes/no) as the outcome and all significant predictors in the primary analysis as independent variables.
All statistical analyses were performed with SPSS statistical software package version 20.0 (SPSS Inc., Chicago, IL) by TG. All P-values calculated were 2-tailed, and the level of significance was set at alfa = .05

Role of Funding Source
This study was not supported by any company or grants. The costs were borne by the authors' institutions.

Results

We selected 155 of a total of 183 trial episodes for our study; the remainder was excluded due to participation in multiple trials (n=28). Two more patients were excluded because they were on placebo while participating; no patient was excluded because they received < 3 months of SA therapy. The general characteristics of the 153 individual patients included in our study population are reported in table 1. Overall, most patients had severe PLD (median liver volume 4974 ml), were female (86%) and received SA therapy for 12 months. The majority of patients had ADPKD as the underlying diagnosis (105 ADPKD versus 48 PCLD). Seventy patients were treated with octreotide LAR 40 mg, whereas 83 PLD patients received lanreotide 120 mg every 4 weeks. For analysis of kidney data, 53 patients were excluded because of a diagnosis of PCLD (n = 48), renal transplantation (n = 4) or incomplete image coverage of kidneys (n = 1). None of the patients underwent liver surgery or transplantation during the trial.

Primary outcome – change in liver volume
Median liver volume decreased from 4974 to 4787 ml in the study population (n=153) after 6-12 months, resulting in a mean change in liver volume of -4.2%. Responses ranged

Table 1: General characteristics

Patients, n	**153**
Trial, n (%)	
LOCKCYST + extension	51 (33)
MAYO + extension	42 (28)
ELATE	32 (21)
RESOLVE	28 (18)
Center, n (%)	
Radboudumc	87 (57)
University Hospital Leuven	24 (16)
Mayo clinic Rochester	42 (28)
Age, y, mean (range)	50 (32 – 70)
Weight, mean (range)	75 (50 -130)
Diagnosis (ADPKD/PCLD)	105/48
Gender (female/male)	132/21
Liver volume, ml, median (range)	4974 (1300 – 15320)
Kidney volume, ml, median (range)[a]	945 (267 – 4566)
Compound (lanreotide/octreotide)	83/70
Everolimus co-therapy (yes/no)	10/143
Duration of SA therapy (6 mo/12 mo)	43/110
Kidney transplantation (yes/no)	4/148
eGFR, ml/min/1.73m^2, mean (range)	70 (19 – 124)
ALP times normal, median (range)	0.8 (0.4 – 5.7)
Elevated ALP (yes/no)	48/104
Bilirubin, µmol/L, median (range)	10 (5 – 33)
Elevated bilirubin (yes/no)	12/141
Gamma-glutamyl transferase, U/L, median (range)[b]	78 (17 – 555)
Elevated gamma-glutamyl transferase (yes/no)	85/26

a Only ADPKD patients
b Included the 111 patients with measured gamma-glutamyl transferase at baseline

from -31.7% to +9.5% in individuals.

The results of the univariate analysis are reported in Table 2. Baseline age, weight, sex, SA type, eGFR and bilirubin status (elevated versus normal) did not affect response during SA therapy in the univariate analysis. Both diagnosis (PCLD vs ADPKD; -1.7%; p = 0.15) and baseline ALP status (elevated vs normal; -2.7%; p = 0.04) were selected for the multivariate analysis. Multivariate linear regression revealed that elevated ALP status at baseline was a significant predictor of liver volume reduction (-2.7%, 95% CI -5.1% to -0.2%, p = 0.04) during SA therapy, whereas diagnosis did not reach statistical significance

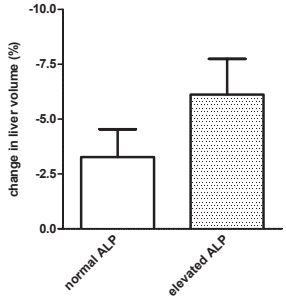

Figure 1: Liver volume reduction according to ALP status. Percent changes in liver volume in 153 PLD patients with normal (n = 105) and elevated ALP (n = 48) at baseline. Data is shown in mean and 95% CI.

Table 2: Univariate and multivariate analysis

Variable	Univariate[a]		Multivariate	
	% change (95% CI)	P value	% change (95% CI)	P value
Age (y), continuous	0.0 (-0.1 to 0.2)	0.60		
Sex, male vs female	1.8 (-1.4 to 5.1)	0.27		
Diagnosis, PCLD vs ADPKD	-1.7 (-4.0 to 0.7)	0.15	-1.3 (-3.6 to 1.1)	0.28
Weight (kg), continuous	0.0 (-0.1 to 0.1)	0.58		
Weight (kg), ≥ or < 75 kg	0.3 (-2.0 to 2.7)	0.77		
SA type, octreotide vs lanreotide	-1.2 (-4.0 to 1.6)	0.39		
eGFR (ml/min/1.73m2), continuous	0.0 (-0.1–0.0)	0.32		
eGFR (ml/min/1.73m2), ≥ or < 60	1.2 (-1.2 to 3.7)	0.34		
	-2.7 (-5.1 to -0.2)	0.04	-2.7 (-5.1 to -0.2)	0.04
Bilirubin, elevated vs normal	2.6 (-1.6 to 6.9)	0.23		
Sensitivity analyses [b]				
Duration of therapy, 12 vs 6 months			-0.7 (-3.3 to 2.0)	0.62
Everolimus co-therapy, yes vs no			-1.5 (-6.1 to 3.3)	0.52
Gamma-glutamyl transferase, elevated vs normal[c]			-1.9 (-4.6 to 0.9)	0.18

[a] All analyses are adjusted for center and baseline liver volume
[b] These variables were included separately to the final multivariate model
[c] Included the 111 patients with measured gamma-glutamyl transferase at baseline

(-1.3%, 95% CI -3.6% to +1.1%; p 0.28). Indeed, mean liver volume reduction was 6.1% (95% CI 2.0% to 4.5%) in patients with elevated ALP, whereas volumes decreased with 3.3% (95% CI 4.5% to 7.7%) in patients with normal ALP (Figure 1). Because baseline liver volume possibly impacted the association between baseline ALP status and change in liver volume, we also checked for interaction, which was absent (p = 0.58).

Next, we added length of treatment and everolimus co-therapy to the multivariate model to test whether these variables affected the primary outcome (Table 1). Treatment duration (12 versus 6 months) was not associated with increased response (-0.7%, 95% CI -3.3% to +2.0%; p = 0.62) in our study population, which supports the decision to aggregate data from the 12 and 6 month treatment studies. Everolimus co-therapy did not affect response during SA therapy (p = 0.47).

Because elevated alkaline phosphatase is also associated with renal osteodystrophy in patients with chronic renal failure, we excluded all patients that had kidney transplantation or had an EGFR < 30 ml/min/1.73m^2 (n = 11) at baseline. Elevated ALP remained associated with response during SA therapy (-3.0%, 95% CI -5.5% to -0.4%; p = 0.03).

Although gamma-glutamyl transferase was not measured in one of the included trials, we checked whether it affected the response in liver volume in the remaining 111 PLD patients by including gamma-glutamyl transferase in the multivariate model. Elevated gamma-glutamyl transferase at baseline did not significantly increase the response in liver volume (-1.9%, 95% CI -4.6% to 0.9%; p = 0.18).

Secondary outcome- change in kidney volume

Median kidney volume decreased from 945 to 932 ml In the 100 ADPKD patients included in the kidney analysis, corresponding with a change of -0.6% (range -15.6% to +22.5%).

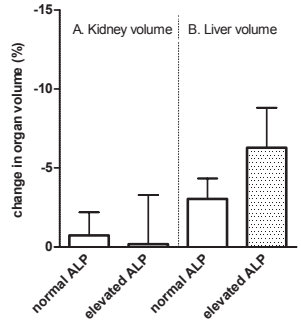

Figure 2: Liver and kidney volume reduction in ADPKD subpopulation according to ALP status. Percent reduction in kidney (A) and liver volumes (B) in 100 ADPKD patients with normal (n = 76) and elevated ALP (n = 24) at baseline. Data is shown in mean and 95% CI.

Multivariate regression analysis again showed that elevated ALP predicted liver volume reduction (-3.2%, 95% CI -6.0% to -0.3%, p = 0.03) in this subgroup, whereas it did not predict kidney volume reduction (+0.1%, 95% CI -3.1 to +3.3%, p = 0.97). Indeed, mean decrease in kidney volume was similar in ADPKD patients with (n = 24) and without (n = 76) elevated ALP at baseline (-0.2% versus -0.7%; Figure 2A), whereas elevated ALP status was still associated with increased reduction in liver volume (-6.3% versus -3.0%; Figure 2B).

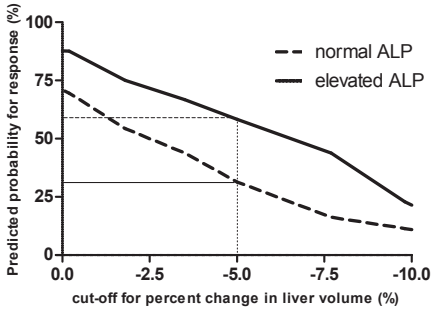

Figure 3: Probability of achieving a good response during SA therapy, stratified for ALP status. This figure shows the probability of achieving a good response during SA therapy using different cut-offs for liver volume reduction. For every cut-off of liver volume reduction, there is a higher probability of achieving this reduction when the patient has an elevated ALP. For example, if you set a reduction of 5% in liver volume as the threshold for response during SA therapy (dotted line), the probability of achieving this response will be 58% for patients with elevated ALP (dashed line) and 31% for patients with normal ALP (connected line).

Probability for good response

We checked whether ALP status also affected the probability of achieving a good response, defined by using different cut-offs for reduction in liver volume (figure 3). As expected, the probability of achieving a good response decreases when the cut-off for good responder is set at a higher threshold. Elevated ALP status increased the chance of becoming a good-responder compared with normal ALP status for all cut-off values. For example, when a reduction of 5% in liver volume is used as a cut-off for good-response during SA therapy, the probability of achieving a good-response will be 58% for patients with elevated ALP at baseline, whereas it will be 31% for patients with normal ALP.

Discussion

The main finding of our study was that baseline elevated ALP increased liver volume reduction in PLD patients during SA therapy, whereas it did not predict kidney volume reduction. SA type, underlying diagnosis and eGFR did not affect responses to SA therapy. The target cell in PLD is the cholangiocyte. While the exact function of ALP is to be

elucidated there is evidence to suggest that ALP affects the secretory function of cholangiocytes. The apical membrane of cholangiocytes are continuously exposed to high ALP concentrations and one study showed that administration of ALP to bile duct ligated rats decreased basal and secretin stimulated bile flow and biliary bicarbonate secretion.[21] The authors suggested that ALP could counterregulate secretory stimulation of cholangiocytes, thereby preventing further increase in bile pressure during obstructive cholestasis.[21]

ALP could exert a similar role in PLD, counteracting fluid secretion from cholangiocytes lining the hepatic cysts, thereby enhancing the effect of SAs on cAMP-dependent chloride and fluid secretion.[22, 23] The conjecture is that elevated ALP plays a protective role in PLD. However, since all patients received SA therapy in this cohort, it remains unclear whether ALP also predicts liver volume reduction in untreated patients.

Several studies found elevated ALP levels in PLD patients (15% to 47%), similar to the proportion (31%) observed in our study.[12, 24, 25] The increase in ALP in PLD probably reflects cholangiocyte activation.[26] In these retrospective studies, patients with elevated ALP were more likely to have an indication for liver transplantation[12] or to have invasive treatment, which suggest a worse prognosis instead of the improvement in liver volume we observed[25]. However, findings in these studies were not adjusted for baseline liver volume. In our cohort, only 13% of patients with a baseline liver volume of less than 3 Liter (25th percentile) had elevated ALP at baseline, in contrast to 60% in patients with a baseline liver of more than 7 Liter (75th percentile). It is therefore more likely that in these retrospective studies the need for therapy was set by severe hepatomegaly rather than the elevated ALP. Our study clearly shows that elevated ALP predicted response in liver volume during SA therapy independently of baseline liver volume.

Whether a better response also translates results in improvement of symptoms remains to be elucidated. Unfortunately, we could not investigate patient reported outcomes in our study because different QoL questionnaires were used in the included trials. In addition, the generic gastrointestinal symptom questionnaire used in some of the trials did not adequately capture and detect changes in PLD related symptoms over time. Recently, a polycystic liver disease specific questionnaire is developed which is more sensitive to change in PLD-specific symptoms than the generic SF-36.[27] This questionnaire can be used in future studies to investigate whether our findings also affect clinical responses.

SA type (octreotide or lanreotide) was not associated with change in response in our study. This is in line with the results of a recent meta-analysis that compared the effect of SA with placebo in PLD patients.[7] Although the clearance of somatostatin analogues partly depends on renal function, we did not find a relation between eGFR or ADPKD diagnosis and change in liver volume in our study. [10] However, most ADPKD patients in our study did not have severe renal insufficiency, which precludes a thorough investigation.

Our results indicate that elevated ALP can serve as a liver-specific biomarker for response in patients requiring SA treatment. At this moment, SAs are used off-label or in the context of clinical trials to highly symptomatic patients unfit for surgical therapies.[28] Given the high costs of SAs, it is preferable to initiate treatment in those patients that will have a high probability for achieving a response. The ALP status can help decide whether to start SA therapy in these patients, thus preventing unnecessary treatment in other patients. Our results need to be confirmed in patients receiving SA therapy over 1 year to confirm

that ALP status also predicts long-term outcomes.

The major strength of our study is that we have collected the largest group to date of individual PLD patients that received long-acting SA therapy for 6-12 months, which enabled us to investigate factors associated with increased response. All included patients were symptomatic or had severe PLD and from different international centers, thus reflecting the patient population that requires treatment. This increases the generalizability of our findings to this group of PLD patients.
A limitation in our study was that we aggregated 6 and 12 months data. However, a sensitivity analysis showed that treatment duration did not affect the change in liver volume. In addition, one of the included studies showed that the decrease in liver volume mainly occurs in the first 6 months, and stabilizes between 6 and 12 months.[13] Second, we did not determine ALP isoenzyme typing to exclude other causes of ALP elevation, including increased osteoblastic activity due to renal osteodystrophy in chronic kidney disease.[29] However, elevated ALP remained a significant predictor for response when ADPKD patients at high risk for renal osteodystrophy (eGFR < 30 ml/min/1.73m^2 or kidney transplantation) were excluded. In addition, 97% of patients with elevated ALP had also an elevated gamma-glutamyl transferase, which makes a hepatic origin of ALP very likely.

In conclusion, elevated ALP is a liver-specific, independent predictor of response in patients with PLD during SA therapy. ALP could serve as a prognostic biomarker in PLD patients requiring SA treatment.

Acknowledgements

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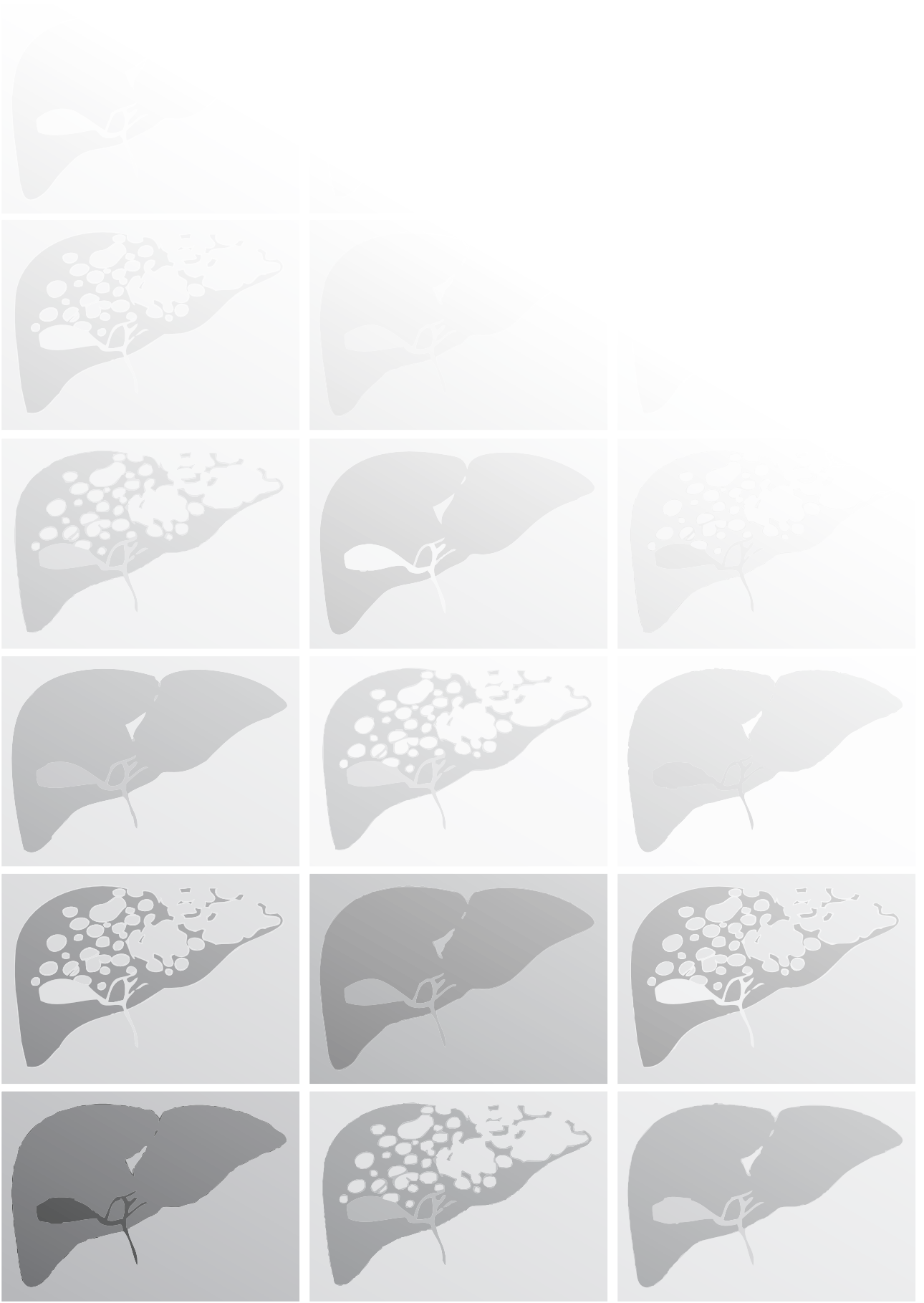

Chapter 6

General discussion and future prospects

General discussion

Currently available treatment options for symptomatic polycystic liver disease (PLD) are aimed at surgical reduction of liver volume.[1] Although these therapies are successful in selected patients, they cause significant morbidity and mortality, and most importantly, are unable to change the natural course of the disease.[2, 3] In many PLD patients with massive hepatomegaly, liver transplantation remains the only treatment option. Although survival after liver transplantation is good compared with other liver disease patients, there is still a high mortality rate of 8% in 5 years.[1, 4]
This has led to the introduction of somatostatin analogues as treatment option for PLD (**chapter 2**). In the last few years, several trials demonstrated the beneficial effects of somatostatin analogues on liver volume in patients with PLD.[5-10] However, given the overall modest effect of therapy, unknown side-effects profiles in subgroups and the uncertainty who will respond, it is still unclear which patients should be treated with this drug.
We investigated several patient, disease and treatment factors that may affect outcomes in PLD patients receiving somatostatin analogues. The goal of this thesis was to identify PLD patients that benefitted most from somatostatin analogue therapy, in order to individualize the treatment approach in these patients.

Answers to research questions

Research question 1: Are somatostatin analogues effective and safe in ADPKD patients?

We demonstrated that 6 months of lanreotide reduced liver and kidney volumes in ADPKD patients and decreased postprandial fullness, shortness of breath and abdominal distension (**chapter 3a&b**). These findings are in line with other studies that evaluated octreotide in ADPKD patients, although these studies did not evaluate symptoms and quality of life.[11, 12] In addition, estimated glomerular filtration rate (eGFR) decreased in the first 4 weeks, stabilized thereafter and declined again after withdrawal of lanreotide. Our results support the hypothesis that lanreotide is effective in reducing liver and kidney volumes in patients with ADPKD, and suggests a protective role of lanreotide in deterioration of renal function. However, the short follow-up and the lack of a control group precluded definite conclusions on renoprotective effects of lanreotide.
We did not find an effect of somatostatin analogue therapy on health-related quality of life in this study. Possible explanations are that reductions in liver volumes and symptoms were too small to result in a change in quality of life, or that the EQOL-5D was unable to detect the tangible changes in quality of life. Indeed, recent studies have demonstrated the low responsiveness of the EQOL-5D for detecting disease progression and treatment response in other chronic conditions.[13, 14] In retrospect, the SF36 would be more appropriate to include as a quality of life endpoint, as several studies showed that this questionnaire can detect decreased quality of life in patients with PLD.[15, 16]
Lanreotide was well tolerated in ADPKD patients, even in the context of reduced eGFR. Three patients were suspected of hepatic or renal cyst infection during our study, all with a history of cyst infections. This number seems high compared with the incidence of cyst infections in ADPKD of one per 100 patients per year.[17] Although cyst infections have

never been related to somatostatin analogues, some animal studies have shown that somatostatin analogues can induce bacterial translocation from the gut.[18, 19] Whether this also results in an increased risk for developing a cyst infection during somatostatin analogue therapy needs to be investigated.

Research question 2: Are there certain patient or disease subgroups with increased responses to somatostatin analogue therapy?

We demonstrated that young female patients (48 years and younger) show the largest response after 6-12 months of somatostatin analogue therapy compared with placebo in **chapter 4**. This large effect is mainly caused by counter-acting the increase in liver volume observed in untreated young women. The observation that female sex is a risk factor for a more severe phenotype is in line with findings of other studies. One study showed that females PCLD patients had higher frequency of liver cysts compared with men, whereas in another study including 238 ADPKD patients the number and size of hepatic cysts was correlated with female sex. [20, 21] Both these studies had a cross-sectional design, and thus were unable to explore the relation between gender and polycystic liver disease progression. Only one other study investigated liver enlargement prospectively in PLD patients, and showed that postmenopausal estrogen replacement was associated with selective liver enlargement in ADPKD patients.[22] We are the first to demonstrate that female gender is associated with increased progression in liver volume, independent of exogenous estrogen use or pregnancies, and that somatostatin analogues are able to reverse this process.

We also discovered that underlying diagnosis (ADPKD or PCLD) and liver size did not affect the treatment efficacy of somatostatin analogues in PLD patients. The absence of a relation between liver volume and treatment effect is in contrast with previous trials that showed that larger livers had more liver reduction than smaller livers.[5, 9] However, these trials investigated absolute liver volume reduction instead of percent changes. Given the large range in liver volumes in our trials (1109 ml – 15,320 ml), correction for baseline volume by using proportional change is more appropriate when investigating volume changes. Proportional change is also commonly used in ADPKD studies that include kidney volume as an outcome.[23]

We identified elevated alkaline phosphatase (ALP) as an independent predictor for liver volume response in PLD (**chapter 5**). ALP has been investigated in several other liver diseases. One study showed that high ALP level acts as a surrogate biomarker for worse prognosis in primary sclerosing cholangitis, whereas in another study decreasing ALP resulted in improved survival in primary biliary cirrhosis patients treated with ursodeoxycholic acid.[24, 25] These findings underline the role of ALP as a biomarker in liver diseases. Our results suggest that ALP can act as a prognostic biomarker in PLD patients requiring somatostatin analogues. We speculate that ALP status can assist in the decision whether to start somatostatin analogue therapy in these patients.

Both octreotide 40 mg and lanreotide 120 mg demonstrated comparable efficacy in reducing liver volumes in our studies. Although formal comparative studies are lacking in PLD, our results are in line with studies that evaluated somatostatin analogues in patients with acromegaly, which demonstrated similar effects of octreotide and lanreotide.[26, 27]

Implications

Somatostatin analogues are effective in attenuating polycystic liver and kidney growth and reducing symptoms in ADPKD, and can therefore be used to treat ADPKD patients with highly symptomatic PLD who are ineligible for surgical therapies. Whether SA therapy is effective and safe in patients with end-stage renal disease needs to be investigated.
Based on our findings, there is no preference for a specific type of somatostatin analogue (lanreotide 120 mg or octreotide 40 mg) when treating PLD patients. Although only a formal randomized trial can definitely conclude which somatostatin analogue type is more effective in PLD, we believe that this thesis provides enough evidence for this recommendation. One study showed that a lower dose of lanreotide (90 versus 120 mg) was also effective in reducing liver volume, although less pronounced.[28] We therefore recommend using the somatostatin analogue doses used in the clinical randomized trials. Especially young women with PLD are at risk for a progressive disease course. This provides extra support for the avoidance of additional risk factors such as exogenous estrogens for young female PLD patients. Given the efficacy of somatostatin analogues in this subgroup, one could consider starting therapy in young women with symptomatic PLD in clinical practice, especially when they have an elevated ALP. Before starting somatostatin analogues, clinicians must first become familiar with side-effects and guidelines of prescribing these drugs in patients with PLD, and have the facilities to perform liver volumetry. In addition, our results only apply for a treatment period of 6-12 months, although two extension trials showed that prolonging somatostatin analogue therapy resulted in maintenance of the effect up to 2 years. [5, 8, 9, 29] Discontinuation resulted in immediate recurrence of liver growth, indicating that continuous treatment will be necessary to maintain the beneficial effect.[29]

Reflection

The main strength of this thesis was that we included the individual patient data of all published trials evaluating long-acting somatostatin analogue therapy in PLD patients. We only included data from prospective studies, which is less sensitive for bias compared with retrospectively collected data. The collaboration and sharing of data with other international research groups maximized the number of patient numbers in our studies, which increased the power of our analyses. PLD is a rare disease, therefore the collaboration with other centers is essential to be able to design and execute the studies described in this thesis.
We used an observational trial design to evaluate the effect and safety of lanreotide in ADPKD patients. Although this trial confirmed the results in other studies, it was of limited added value to current existing evidence. One could consider the choice for an observational design as a limitation, because it is difficult to draw definite conclusions without a control and treatment effects may be overestimated. We believe that the inclusion of a control group would not be ethical, because there already was evidence that lanreotide reduced liver and kidney volumes in a small group of patients with ADPKD.[5] In my opinion, an observational design was more appropriate than a formal placebo-controlled trial to investigate effects and safety of somatostatin analogues in this specific subgroup of patients. However, the short follow-up period of 6 months and strict inclusion

and exclusion criteria limited the novelty of our observational study. By including patients with end-stage renal disease, we could obtain more information on safety and effect of somatostatin analogues in certain patient groups that were excluded in the original trials. By extending the time of follow-up we would be able to draw conclusions on effects and safety beyond 6 months.
We used a non-validated generic gastrointestinal questionnaire to measure (changes in) PLD-related symptoms in most studies.[30] This questionnaire is probably less responsive to the specific nature of PLD and is therefore limited in detecting effect of SAs on symptoms in PLD. Unfortunately, a standard validated questionnaire that scores PLD-related symptoms in patients with ADPKD or PCLD was not available at the start of these studies.

Future perspectives

The results of clinical trials in PLD suggest that lifelong treatment with somatostatin analogues might be necessary to maintain its effects. It is therefore most important to determine whether the beneficial effects in young women and safety profiles are maintained with long-term therapy, especially given the considerable costs of this treatment and the risk for developing cholelithiasis after prolonged treatment with somatostatin analogues.[31, 32] The DIPAK trial evaluates the effect of lanreotide in 300 ADPKD patients over a time period of 3 years and includes a considerable group of patients with PLD. These results of this study will provide more insight in the long-term efficacy and safety of lanreotide in PLD.[33]
Future studies should focus on enhancing the efficacy of somatostatin analogues. Attempts to increase efficacy by adding the mTOR-inhibitor everolimus unfortunately failed.[7] Pasireotide is a novel multireceptor synthetic somatostatin analogue.[34] In contrast to lanreotide and octreotide, it binds with high affinity to all somatostatin receptors except for somatostatin receptor 4.[35] The SOM230 study currently investigates the efficacy of pasireotide in patients with severe PLD (NCT01670110). The further unraveling of molecular mechanisms in hepatic cystogenesis will aid in the identification of new therapeutic strategies.[36] This had led to the discovery of ursodeoxycholic acid as a potential medical therapy for PLD, which is currently being investigated in the CURSOR trial (NCT02021110).
Little is known about the progression and consequence of hepatomegaly in PLD patients. We should prospectively investigate prognosis of individual PLD patients, in order to identify patients with worse prognosis that require therapy. Endpoints of interest would be symptoms, complications, liver volume and therapies. Ideally, the study will be a large long-term prospective cohort running in multiple international centers. This study will enable us to answer important clinical research questions, such as the role of postmenopausal status in PLD progression and risk factors for massive hepatomegaly in men. Finally, we can use this study design to further explore the role of alkaline phosphatase as a prognostic biomarker in treated and untreated PLD patients.
While our volumetry method (manual segmentation) accurately calculates liver volumes, it is also very time-consuming. We should therefore develop automatic volumetry methods that can measure liver volumes quickly, accurately and with good reproducibility. A recent study used ellipsoid equation to reliably estimate total kidney volumes in ADPKD patients.[37] This procedure can possibly be adapted in order to estimate liver volumes

in PLD. In addition, we should improve current volumetry techniques so that they can determine liver cyst volumes in addition to total liver volumes. This will enable us to investigate how drug therapies affect different tissues in the polycystic liver.
It remains an important issue that the indication for treating PLD patients is dictated by symptoms rather than by liver volume per se. It is still unknown to which extent progression in liver volumes results worsening of symptoms and quality of life, and vice versa which reduction in liver volume translates into significant clinical improvement. Unfortunately, current gastrointestinal symptom questionnaires lack specificity for PLD as they also include items that are irrelevant and do not address extra-abdominal symptoms in PLD, which makes it difficult to investigate the relationship between liver volume and clinical improvement. Recently, a tool is developed which is more sensitive to changes in PLD-specific symptoms than the generic SF-36.[38] This patient-reported outcome tool can be utilized in future studies to evaluate the efficacy of (experimental) therapies and to define clinical response in patients receiving somatostatin analogue therapy.

RESEARCH AGENDA

- EVALUATE LONG –TERM EFFICACY AND SAFETY OF SOMATOSTATIN ANALOGUES IN PLD
- INVESTIGATE THE EFFICACY OF PASIREOTIDE IN CLINICAL TRIALS
- FURTHER EXPLORE MOLECULAR MECHANISMS IN HEPATIC CYSTOGENESIS TO IDENTIFY NEW THERAPEUTIC STRATEGIES
- FOLLOW THE NATURAL COURSE OF PLD PATIENTS AND IDENTIFY PATIENTS AT RISK FOR WORSE PROGNOSIS
- INVESTIGATE THE ROLE OF ALKALINE PHOSPHATASE AS A PROGNOSTIC BIOMARKER IN TREATED AND UNTREATED PLD PATIENTS
- DEVELOP FAST AND ACCURATE METHODS TO MEASURE TOTAL LIVER AND LIVER CYST VOLUME PROGRESSION
- UTILIZATION OF A PLD-SPECIFIC PATIENT-REPORTED OUTCOME TOOL IN FUTURE STUDIES
- DEFINE CLINICAL RESPONSE IN PLD PATIENTS RECEIVING SOMATOSTATIN ANALOGUE THERAPY

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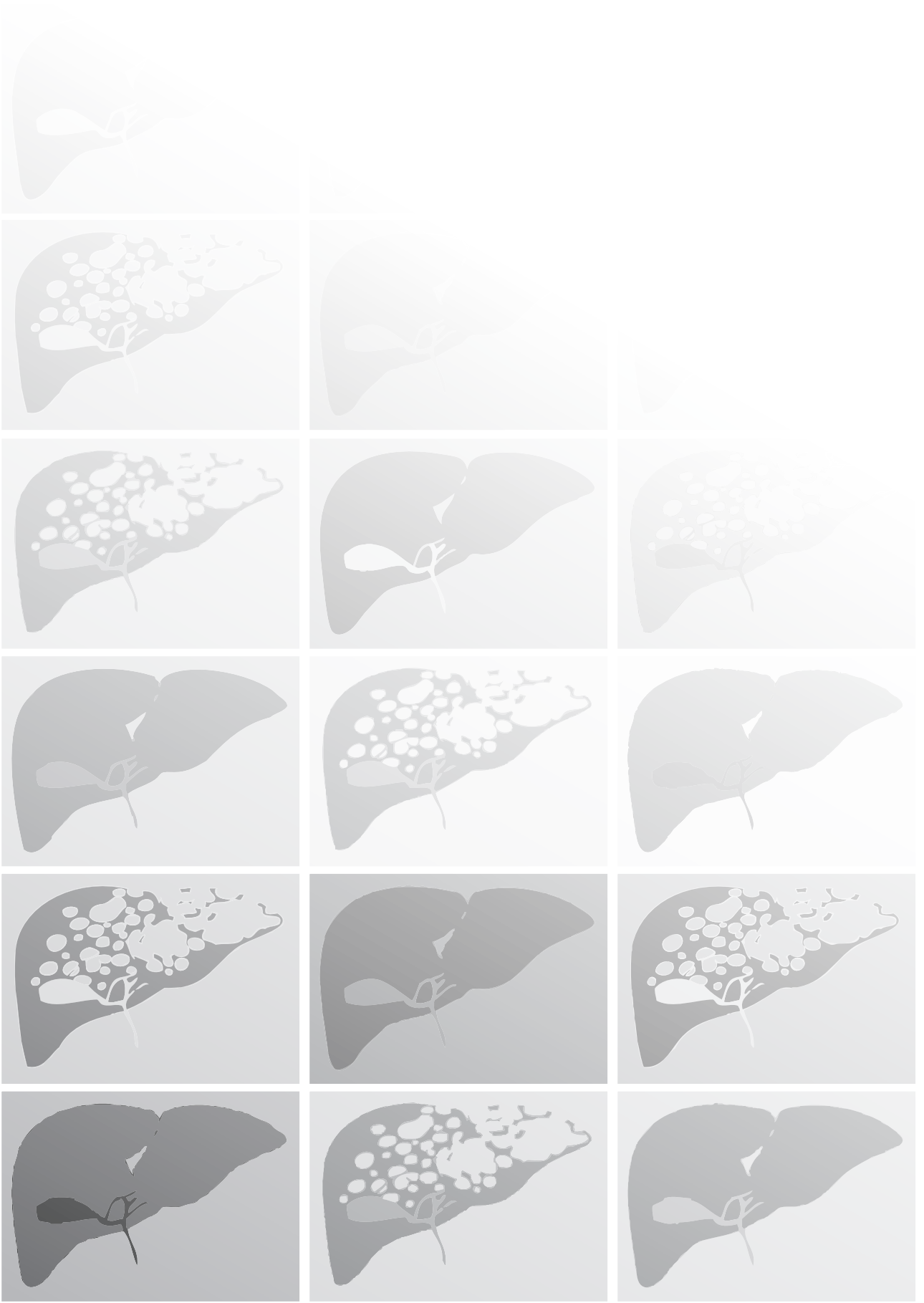

Chapter 7

Summary and Acknowledgements

English Summary

Polycystic liver disease (PLD) is characterized by the formation of multiple benign cysts in the liver. It is associated with two inherited disorders: combined with polycystic kidneys in autosomal dominant polycystic kidney disease (ADPKD) and isolated in autosomal dominant polycystic liver disease (PCLD). The natural course of PLD shows a continuous growth in number and size of hepatic cysts. Although liver function is preserved, the massive enlarged liver can result in mechanical complaints, including abdominal distension, pain, and early satiety. Currently available treatment options are mainly invasive and are aimed at surgical reduction of liver volume in order to ameliorate symptoms. These therapies are successful in selected patients. However, they can cause significant morbidity and mortality, and most importantly, are unable to change the natural course of the disease.

This has led to the introduction of somatostatin analogues as a treatment option for PLD. Somatostatin analogues, including lanreotide and octreotide, are cyclic adenosine monophosphate (cAMP) inhibitors and decrease hepatic cyst volumes. In the last few years, several trials have demonstrated that somatostatin analogues reduce polycystic liver volumes in patients with PLD (**chapter 2**). These observations clearly support the thesis that growth of polycystic livers can be suppressed by somatostatin analogues.

However, there are still some issues that need to be resolved before somatostatin analogues can be used in daily practice. A more pronounced side-effect profile can possibly off-set potential benefits of therapy and limits its use in clinical practice. In addition, it is too costly to prescribe somatostatin analogues to every patient with PLD. Given the overall modest effect of somatostatin analogues in trials, it is paramount to investigate whether there are subgroups of PLD patients who will benefit more from this therapy.

In this thesis, we investigated several patient factors (age, gender), disease characteristics (liver size, underlying diagnosis, lab abnormalities) and treatment variables (somatostatin analogue type) that may affected outcomes in PLD patients receiving somatostatin analogue therapy. These findings will help us to prevent unnecessary or ineffective somatostatin analogue therapy in PLD patients, as well as individualizing treatment strategies.

To investigate the safety and effect of somatostatin analogue therapy in ADPKD patients with PLD, we performed an observational trial that evaluated 6 months of lanreotide in 43 ADPKD patients with polycystic livers (**chapter 3a & 3b**). Patients had reduced polycystic liver and kidney volumes and decreased gastro-intestinal symptoms after 6 months of lanreotide treatment, with an acceptable side-effect profile. However, we did not find an effect on quality of life in this study. Our results suggest that lanreotide therapy can be used to treat symptomatic PLD in ADPKD patients.

In **chapter 4** we investigated whether certain subgroups of PLD patients would benefit more from somatostatin analogue therapy. We pooled the individual patient data of all

randomized placebo-controlled trials that evaluated somatostatin analogues in PLD and had liver volume as the primary outcome. Key findings of our meta-analysis were that underlying diagnosis (ADPKD or PCLD) and liver size had little influence on efficacy of somatostatin analogues in PLD patients. Particularly placebo-treated young women (48 years old and younger) showed the largest increase in polycystic liver volume (+4.8%) and responded best to somatostatin analogue therapy (-8.0%) when compared with placebo. Based on these results, one could consider to start somatostatin analogue therapy in young women with PLD.

Finally, to identify which factors predict response in PLD patients during somatostatin analogue therapy (**chapter 5**), we pooled the individual patient data of 4 trials (n = 153). Elevated alkaline phosphatase at baseline was an independent predictor for liver volume response in PLD patients treated with somatostatin analogues, but did not predict kidney volume response. Our findings suggest that alkaline phosphatase could serve as a prognostic biomarker in PLD patients requiring somatostatin analogue therapy. It remains unclear whether elevated alkaline phosphatase also predicts liver volume reduction in untreated PLD patients.

These findings confirm the efficacy of somatostatin analogues in different patient groups with PLD, and show that outcomes in PLD can be affected by patient factors (young women) and disease characteristics (alkaline phosphatase). Future studies should focus on patient reported outcomes in PLD, as the main goal of treatment is to improve the quality of life of these patients. Furthermore, since PLD is a chronic condition, it is paramount to confirm the long-term efficacy and safety of somatostatin analogues.

Nederlandse Samenvatting

Polycysteuze leverziekte (PLD) wordt gekenmerkt door de vorming van multipele goedaardige cysten in de lever. Het komt met name voor bij twee erfelijke aandoeningen: in combinatie met polycysteuze nieren bij autosomaal dominant polycysteuze nierziekte (ADPKD) en als een geïsoleerde polycysteuze lever bij autosomaal dominante polycysteuze leverziekte (PCLD). Het natuurlijk beloop van PLD toont een continue groei in grootte en aantal van levercysten. Hoewel de leverfunctie gespaard blijft, kan de massaal vergrote lever leiden tot mechanische klachten, zoals een uitgezette buik, pijn en snelle verzadiging. De op dit moment beschikbare behandelingen zijn voornamelijk chirurgisch en gericht op volumereductie van de lever ter vermindering van klachten. Deze behandelingen zijn succesvol bij sommige patiënten. Ze kunnen echter aanzienlijke complicaties en sterfte veroorzaken en, het belangrijkst, ze zijn niet in staat zijn om het natuurlijke beloop van de ziekte te veranderen. Dit heeft geleid tot de introductie van somatostatine analogen als behandelingsoptie voor PLD. Somatostatine analogen, zoals octreotide en lanreotide, kunnen het levercyste volume verminderen door cyclisch adenosine monofosfaat (cAMP) te remmen. Verschillende studies hebben in de afgelopen jaren aangetoond dat somatostatine analogen inderdaad het polycysteuze levervolume kunnen reduceren in PLD patiënten (hoofdstuk 2). Deze waarnemingen ondersteunen duidelijk de stelling dat de groei van polycysteuze levers kan worden onderdrukt door somatostatine analogen.

Er zijn echter nog enkele problemen die moeten worden opgelost voordat somatostatine analogen kunnen worden gebruikt in de dagelijkse praktijk. Een meer uitgesproken bijwerkingenprofiel kan een eventueel voordeel van de behandeling teniet doen. Bovendien is het te duur om alle PLD patiënten somatostatine analogen voor te schrijven. Gezien het gemiddelde effect van somatostatine analogen in studies bescheiden is, is het van groot belang te achterhalen of er subgroepen van PLD patiënten zijn die meer baat hebben bij deze therapie.

In dit proefschrift onderzocht ik verschillende patiëntfactoren (leeftijd, geslacht), ziektekenmerken (grootte van de lever, onderliggende aandoening, laboratorium afwijkingen) en behandelingsvariabelen(somatostatine analoog type) die mogelijk uitkomsten kunnen beïnvloeden bij PLD patiënten die behandeld worden met somatostatine analogen. Deze bevindingen zullen ons helpen om onnodige of ineffectieve therapie met somatostatine analogen in PLD patiënten te voorkomen, en zal zorgen voor verdere individualisatie van behandelstrategieën.

Om de veiligheid en het effect van somatostatine analogen bij ADPKD patiënten met PLD te onderzoeken, voerde ik een observationele trial uit waarin wij 6 maanden behandeling met lanreotide evalueerde in 43 ADPKD patiënten met een polycysteuze lever (hoofdstuk 3a & 3b). Patiënten hadden afgenomen polycysteuze lever- en niervolumes en minder gastro-intestinale symptomen na 6 maanden behandeling met lanreotide, met een acceptabel bijwerkingenprofiel. We hebben echter geen effect op de kwaliteit van leven gevonden. Deze resultaten suggereren dat lanreotide therapie kan worden gebruikt om ernstig symptomatische PLD in ADPKD patiënten te behandelen.

In hoofdstuk 4 heb ik onderzocht of bepaalde subgroepen van PLD patiënten beter reageren op somatostatine analoog behandeling. Ik heb de individuele patiëntgegevens samengevoegd van alle gerandomiseerde placebogecontroleerde studies die de effectiviteit van somatostatine analogen hebben onderzocht in PLD patiënten, en levervolume als belangrijkste uitkomst hadden. Deze meta-analyse liet zien dat onderliggende diagnose (ADPKD of PCLD) en levergrootte weinig invloed hadden op effectiviteit van somatostatine analogen in patiënten met PLD. Met name jonge vrouwen (48 jaar en jonger) behandeld met placebo lieten de grootste stijging in polycysteuze lever volume (+ 4,8%) zien en reageerden het best op somatostatine analoog behandeling (-8,0%). Gebaseerd op deze resultaten kan men overwegen jonge vrouwen met PLD te behandelen met somatostatine analogen.

Tenslotte heb ik de individuele patiëntgegevens van 4 studies (n = 153) samengevoegd om te bepalen welke factoren respons voorspellen bij PLD patiënten tijdens somatostatine analoog behandeling (hoofdstuk 5). Een verhoogd gehalte aan alkalische fosfatase (een leverenzym dat verhoogd is bij PLD patiënten) bij start van behandeling was een onafhankelijke voorspeller voor lever-volume afname in PLD patiënten behandeld met somatostatine analogen, maar was geen voorspeller voor nier-volume afname. Deze bevindingen suggereren dat alkalische fosfatase zou kunnen dienen als een prognostische biomarker voor lever-volume respons in PLD patiënten die behandeld gaan worden met somatostatine analogen. Het blijft onduidelijk of verhoogde alkalische fosfatase ook lever volume afname voorspelt in onbehandelde PLD patiënten.

Deze bevindingen bevestigen de werkzaamheid van somatostatine analogen in verschillende patiëntengroepen met PLD, en tonen dat de response op somatostatine analogen kunnen worden beïnvloed door patiëntfactoren (jonge vrouwen) en ziektekenmerken (alkalisch fosfatase). Omdat het verbeteren van kwaliteit van leven in PLD patiënten het belangrijkste doel van behandeling is, zal toekomstig onderzoek zich meer moeten richten op patiënt gerapporteerde uitkomsten. Aangezien PLD een chronische aandoening is, is het noodzakelijk dat de werkzaamheid en veiligheid van somatostatine analogen op lange termijn bevestigd worden.

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Curriculum Vitae

Naam:	Tom Gevers
Woonplaats:	Nijmegen
Geboortedatum:	04-10-1982

Tom Gevers werd op 4 oktober 1982 geboren in Nistelrode en groeide hier op in een gezin met twee jongere zusjes. Na het behalen van het Atheneum diploma aan het Udens College te Uden, startte hij in 2001 met de studie Biomedische Wetenschappen aan de Radboud Universiteit Nijmegen (RUN). Tijdens het afronden van deze studie startte hij met de studie Geneeskunde in 2007, ook aan de RUN.

Na het behalen van zijn artsexamen in juli 2011 is Tom begonnen met zijn promotieonderzoek, waarin hij de toepassing van somatostatine analogen bij patiënten met polycysteuze leverziekte onderzocht onder supervisie van zijn promotor prof. J.P.H. Drenth. Tijdens zijn promotieonderzoek heeft hij het Radboud Da Vinci talent programma gevolgd en heeft hij 2 maanden in de Mayo Clinic (Rochester, MI, USA) gewerkt.

In het kader van zijn opleiding tot Maag- Darm- Leverarts, begon Tom op 1 juli 2014 aan zijn vooropleiding Interne Geneeskunde in het Rijnstate ziekenhuis te Arnhem (opleider dhr. dr. Louis Reichert).

Tom woont samen met zijn verloofde Femke Brants in Nijmegen, en ze gaan later dit jaar trouwen.

List of publications

2010: Bruinsma IB, te Riet L, **Gevers TJ**, et al. Sulfation of heparan sulfate associated with amyloid-beta plaques in patients with Alzheimer's disease. Acta Neuropathol. 2010; 119(2):211-20

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