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Safety and efficacy of different lanreotide doses in the treatment of polycystic liver disease: pooled analysis of individual patient data

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SUMMARY

Background
Long-acting lanreotide (LAN) 120 mg every 4 weeks reduces liver volume (LV) in patients with polycystic liver diseases (PCLD). Animal studies demonstrated that the inhibition of hepatic and renal cystogenesis is dose dependent.

Aim
To investigate the safety and efficacy of two different LAN doses in PCLD patients.

Methods
The 6-month results of the LOCKCYST I trial, its extension study and the LOCKCYST II trial were pooled. LV at baseline and month 6 was measured by CT-scan and blindly re-analysed by two independent radiologists.

Results
The study population [132 treatment periods, age 49 years (IQR: 45-55), 114 women] consisted of three groups. Each received treatment every 4 weeks during 6 months: placebo (n = 26); LAN 90 mg (n = 55) or LAN 120 mg (n = 51). The inter-observer variability and agreement in the calculation of LV were excellent. Severe side effects occurred with placebo, LAN 90 mg and LAN 120 mg in respectively 0%, 7% and 16%. Change in LV's after 6 months in these three groups were respectively: increase of +36 mL [(−45)–(+138)]; decrease of −82 mL [(−285)–(+92)] and decrease of -123 mL [(−312)–(+4)] (Kruskal-Wallis One Way ANOVA on Ranks; P = 0.002). Based on ROC analysis, a reduction of ≥120 mL in LV has a positive predictive value of 64% for improving symptoms (ROC analysis AUC: 0.729; sensitivity 73%, specificity 69%, $P < 0.0001$).

Conclusions
Both LAN 90 mg and LAN 120 mg reduce liver volume. LAN 90 mg has less side effects. This suggests that in case of intolerance to LAN 120 mg, a dose reduction to LAN 90 mg is meaningful.

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INTRODUCTION

Polycystic liver disease (PCLD) is a chronic disorder in which numerous fluid-filled hepatic cysts are scattered throughout the liver. PCLD results from two inherited disorders: autosomal dominant polycystic kidney disease (ADPKD) or isolated polycystic liver disease (ADPCLD). ADPKD is the most common inherited nephropathy and the second most common inherited syndrome, affecting 1/800–1000. It is characterised by a progressive development and enlargement of cysts originating from the nephrons, leading to renal failure in 50% of the affected patients. In addition, during their lifetime 83% of these patients also develop liver cysts.[1, 2] Patients suffering from ADPCLD only present with liver cysts. The natural history of PCLD, regardless of the genetic mutation, is similar.[3]

Most of the patients with PCLD are asymptomatic, but in 2–5% the expansion of liver cysts leads to symptomatic hepatomegaly. Symptoms include abdominal distension, early satiety, dyspnoea and abdominal pain. PCLD may lead to severe malnutrition, portal hypertension and can be lethal. Liver cysts themselves display also their intrinsic complications: bleeding, infection and/or rupture.[3, 4] Surgical treatment aims to reduce liver volume (LV) and includes a variety of procedures such as aspiration-sclerotherapy, laparoscopic or laparotomic fenestration and partial liver resection.[5] The drawbacks common to all of these procedures are that they are only partial effective; that they have a high morbidity and most importantly that they do not change the natural course of the disease. Indeed, in the majority of the patients, the symptoms recur due to the growth of new cysts or re-growth of treated cysts. In addition, they are sometimes technically not possible and therefore liver transplantation is sometimes the only real solution.[6, 7]

Medical treatment became only recently available. In this regard, preclinical studies in the PCK rat (a recessive model of polycystic kidney and liver disease) showed that the somatostatin analogue (SS-analogue) octreotide (Novartis Pharma, Basel, Switzerland) slows the progression of hepatorenal cystogenesis by reducing 3′-5′-cyclic adenosine monophosphate levels in kidney and in bile ducts. In the preclinical animal studies with octreotide, the inhibition of hepatic and renal cystogenesis was dose dependent.[8] In a randomised, placebo-controlled trial, we showed that lanreotide Autogel (LAN) (somatuline, Ipsen Pharma, Beaufour, France) 120 mg is superior to placebo for the treatment of PCLD by reducing LV and improving aspects of quality of life.[9] Similar data in humans were obtained using octreotide Long Acting Release with a dose of 40 mg (octLAR 40 mg).[10–12]

It is not known which dose of somatostatin analogues is needed to establish a volume reducing effect. This is relevant as higher doses of somatostatin analogues have inherent side effects. Well known side effects are steatorrhea, abdominal cramps and flatulence on the short term and gall-bladder stones on the long term.[13] The optimal dose (efficacy vs. side effect balance) of somatostatin-analogues in the treatment of PCLD in patients has never been investigated.

In the present study, we explored the safety and the efficacy of two different doses of LAN: 90 mg and 120 mg for the treatment of PCLD and the degree of volume reduction which offers symptomatic improvement.

MATERIALS AND METHODS

Study design

In our previous placebo-controlled study, we observed that after 6 months more than 50% of the patients had a reduction in LV of 100 mL or more when they received treatment of LAN 120 mg. Based on these data, we hypothesised that a 100 mL reduction in LV would be achieved in 40% of the patients treated with LAN 90 mg. A power calculation for a randomised study design to demonstrate a dose-dependent effect showed that each arm needed to contain 384 patients (significance level 5%; power 80%; 2-sided). As symptomatic PCLD is a rare disorder, it is unrealistic to recruit and randomise such a high number of patients in an acceptable time period. Therefore, we decided to pool the individual data of the LOCKCYST I trial (clinical trials.gov identifier NCT00565097) and the 6 months data of its extension study (clinical trials.gov identifier NCT00771888), and the data of the first 6 months of the ongoing LOCKCYST II trial (clinical trials.gov identifier NCT01315795).

Study population

The patients enrolled in this study were followed in either one of the collaborating universities: (i) University Hospitals KULeuven, Belgium; (ii) Radboud University Nijmegen Medical Centre, the Netherlands; and (iii) Université Catholique de Louvain, Brussels, Belgium.

Fifty-four patients were enrolled in the LOCKCYST I trial from October 2007 till February 2008. In this randomised, double-blind, placebo-controlled trial, 27 patients were assigned to placebo and 27 to LAN

120 mg. One female patient, who was randomly assigned to placebo, withdrew after 14 weeks because she was diagnosed with breast carcinoma. In the open-label observational extension study of the LOCKCYST I trial, 24 patients who had received placebo in the initial study were crossed over to LAN 120 mg (from April 2008 till February 2009). The data of the first 6 months of these patients were added to the study population. Finally, 57 patients were included between January 2011 and July 2012 in the LOCKCYST II trial, an open-label clinical study to evaluate the safety and efficacy of LAN 90 mg, including a dose escalation to LAN 120 mg in case of nonresponder. The data of the first 6 months in which patients were treated with LAN 90 mg/4 weeks trial during 6 month were added to the study population. Two patients, who tolerated the treatment but received a LT before the 6 month follow-up visit, were excluded from this study. All CT-scans were blindly re-analysed in a nonpaired way. Baseline characteristics (age, body weight, renal function) were systematically adjusted to the treatment episode. We recruited three groups of patients: (i) placebo group (n = 26); (ii) LAN 90 mg group (n = 55); (iii) and LAN 120 mg group (n = 51). A comprehensive overview of the pooled patients' data is given in Figure 1.

End points

The primary end points of this study were to investigate the safety and the efficacy on LV of two doses of LAN. We further investigated the minimal reduction in LV which resulted in an improvement of the symptoms of the patients and the predictors of response to treatment with LAN. Secondary end points were the relative change in kidney volume (KV) and changes in glomerular filtration rates (eGFR) [Modification of Diet in Renal Disease (MDRD), mL/min/1.73 m^2].

Measurement of volumetry

All patients underwent CT-scanning without contrast enhancement by the same device at enrollment and after 6 months. The CT-scans were performed on different multidetector CT-scanners as available at the participating centres: Siemens Somatom Sensation 16 (Radboud University; Nijmegen Medical Centre); Siemens Somatom Sensation 64 and Siemens Somatom Definition Flash (University Hospitals KULeuven) all from Siemens

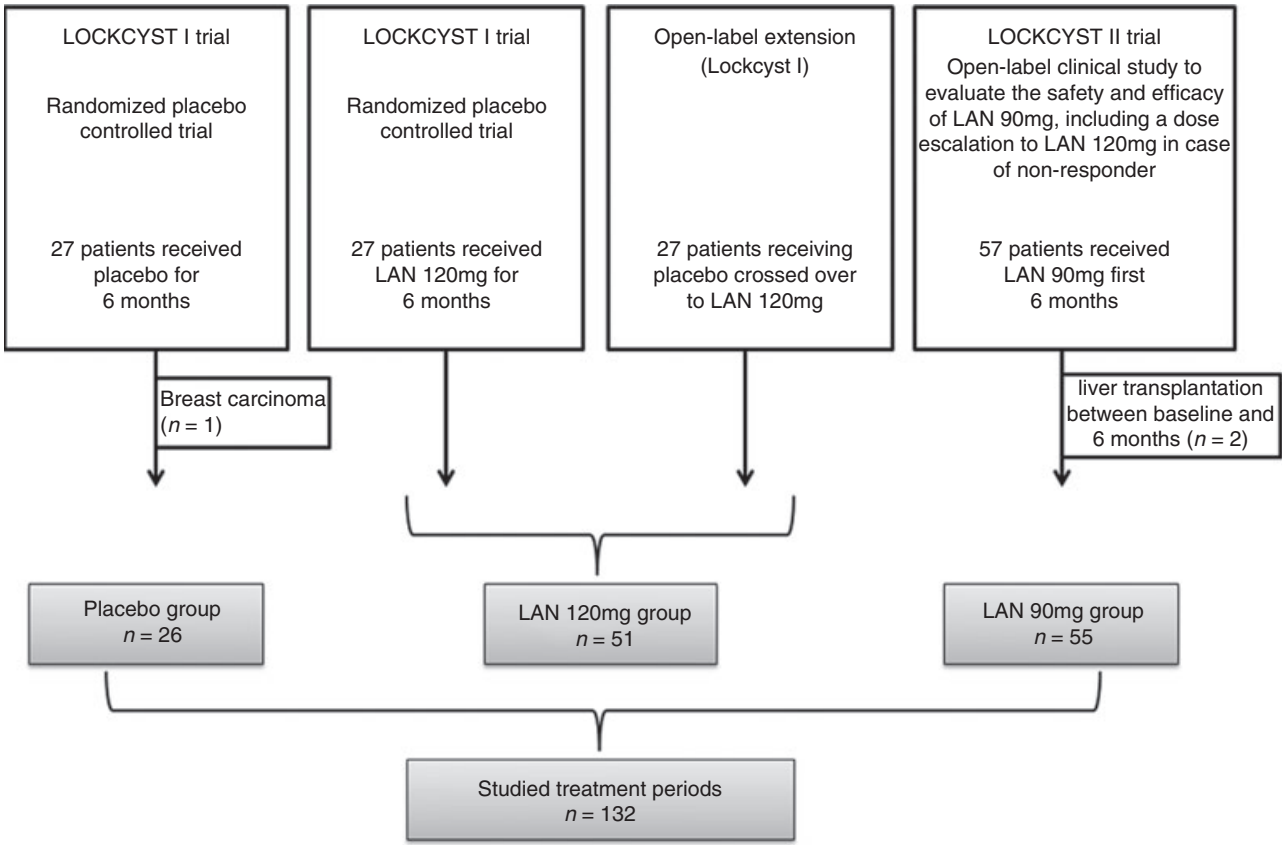

Figure 1 | Overview of the studied treatment periods (n = 132).

Medical Solutions AG, Erlangen, Germany) and Spiral/Helical CT Brilliance 64 (Philips) (Université Catholique de Louvain, Brussels, Belgium). All CT-scans were pooled and blindly re-scored in a nonpaired way. For accurate LV determination, we compared two different software program approaches used for measuring LV's and appreciated their agreement in observing changes of LV in time, assessed by two independent radiologists (CW and VR). All values were measured with the following two software programs: Volume (Siemens, Erlangen, Germany; MMWP), a validated software program which reconstructs the margins of the liver to calculate volume (cm^3) based on density Hounsfield Units [(−15)–(+125)] and a software program compiled in MeVisLab that calculates volumes after reconstruction based on measured surfaces for each slice image of interest. The studies were approved by the institutional review boards of the participating institutions according to their national guidelines. All patients provided written informed consent.

Assessment of symptoms

To date, there is no standard validated questionnaire for PCLD patients to score their symptoms. For each patient, symptoms and complaints of which we interpreted them to be PCLD were noted at baseline (i.e. abdominal distention/pain, early satiety, dyspnoea). At month 6, at the moment that both patient and investigator were not aware of the results of the volumetry, patients were systematically asked whether their symptoms aggravated or stayed similar (clinical *non*responder) or improved under treatment (clinical responder). This information was compared with the changes in LV at 6 months.

Statistical analysis

Statistical analysis was performed on all data using SAS statistical software version 9.2. Baseline characteristics and all volumes are given in median values and interquartile ranges (IQR). To describe the inter-observer variability and better appreciate the agreement in calculating LV over time between both independent observers using different software, Pearson correlation and Bland Altman plots were used. Absolute and percentage changes in LV and KV were assessed, respectively delta LV and delta KV. Changes in LV and KV in the three groups were compared by using Kruskal-Wallis One Way Analysis of Variance (ANOVA on ranks). Dunn's method was used to perform pairwise multiple comparisons. To compare percentage of observations between groups, Chi-square and Fisher's exact tests were used where appropriate. A one-stage approach was used to fit a regression model to the pooled dataset. ROC analysis was performed to define the minimal reduction in LV which results in an improvement of the symptoms of the patients. The *P*-value level of significance was set at 0.05 and all tests are performed at 2-sided significance level.

RESULTS

Inter-observer variability and agreement between the two techniques of volumetry measurement

Pearson correlation for the inter-observer variability of the LV at baseline and at 6 months were respectively R: 0.92 ($P < 0.0001$) and R: 0.96 ($P < 0.0001$). Bland-Altman plots showed that the difference in LV assessment between the two methods was 70 mL (95% CI: 21–119) at baseline and 81 mL (95% CI: 47–114) after 6 months. Bland-Altman plot of the calculated change in LV revealed a mean difference of 31 mL (95% CI: 3–58). There was no proportional error and the variation did not depend on the magnitude of the measurements (Figure 2).Therefore, we proceeded to use a single method (Software Volume; radiologist: CW) to perform further analysis.

Baseline characteristics of the study population

The characteristics of the study population (treatment episodes: $n = 132$) are given in Table 1. There was no difference between the three groups at baseline with one exception regarding the ratio of ADPKD/ADPCLD.

Adverse events and dropouts

Side effects were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria.[14] Mild diarrhoea was defined as grade 1–2; severe diarrhoea as grade 3–4. Severe abdominal cramps were defined according to pain category ≥ grade 2. In addition, a serious adverse event was defined as an event for which the patient needed to stop the therapy and/or needed pancreatic enzyme replacement therapy. As we did not have data about the efficacy of LAN 90 mg, dose reduction was not performed. In the placebo group ($n = 26$), three patients reported the occurrence of mild diarrhoea, but none of them stopped therapy. In the LAN 90 mg group, four patients (7%) developed serious adverse events and this was due to severe abdominal cramps ($n = 1$) and steatorrhea ($n = 3$).One patient suffered from severe hair loss. In the LAN 120 mg group, eight patients (16%) developed a serious adverse event. The side effects as reported by the patients in the placebo, LAN 90 mg group, and LAN

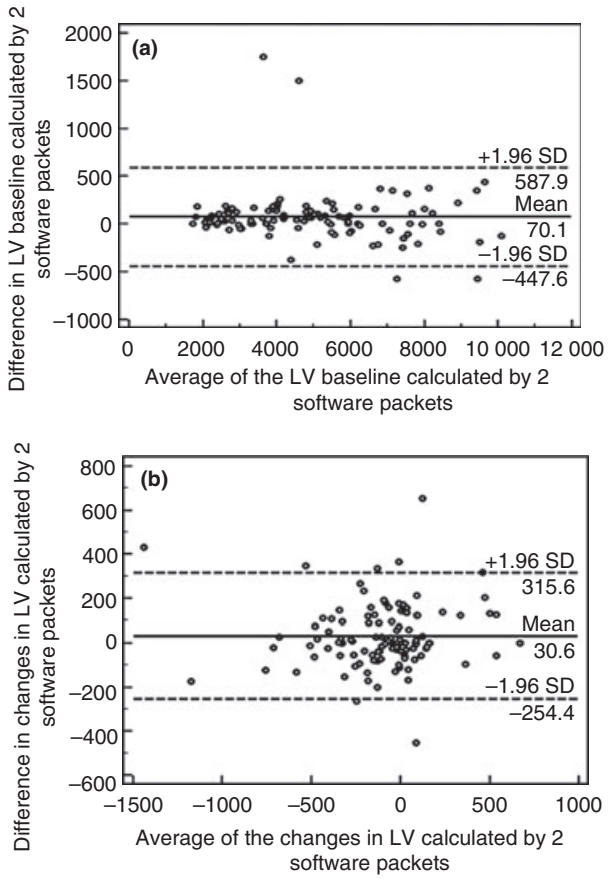

Figure 2 | Bland-Altman plots to appreciate agreement in calculating liver volume (LV) by two different software programs: Volume and software compiled in Mevislab. Panel A shows plot of the LVs baseline. Difference in assessment between the two methods was 70 mL (95% CI: 21–119). Panel B shows the plot of the calculated changes in LV revealing a mean difference of 31 mL (95% CI: 3–58). There was no proportional error and the variation did not depend on the magnitude of the measurements.

120 mg group are given in Table 2. A less pronounced side effect profile can be observed in the group with the lower LAN dose.

Change in liver volume from baseline to 6 months

Paired observations were obtained in respectively 26 patients under placebo, 51 patients treated with LAN 90 mg and 51 treated with LAN 120 mg. Changes in LV's after 6 months in the placebo, LAN 90 mg and LAN 120 mg group were respectively: increase of +36 mL [(−45)–(+138)]; decrease of −82 mL [(−285)–(+92)] and a decrease of −123 mL [(−312)–(+4)] (Kruskal-Wallis One Way ANOVA on Ranks; $P = 0.002$). Relative changes in LV were respectively increase of +1.1% [(−1.2)–(+2.7)] in the placebo group; decrease of −1.4% [(−5.2)–(+1.6)] in LAN 90 mg group and of −2.8% [(−5.1–(+0.1)] in the LAN 120 mg group (Kruskal-Wallis One Way ANOVA on Ranks; $P = 0.002$). Box plot analysis of the median delta LV (mL) in LV in the three groups is given in Figure 3. For a median LV at baseline, the estimated reductions in delta LV are 195 mL (standard error: 67 mL; P unadjusted = 0.004) and 246 mL (standard error: 55 mL; P unadjusted <0.0001) larger with LAN 90 mg and LAN 120 mg respectively, as compared to placebo. The estimated reduction in change in LV for comparison of LAN 90 mg vs. LAN 120 mg is 51 mL (standard error 60 mL; P unadjusted = 0.4). There was no difference in the degree of volume changes between blinded and open studies ($P = 0.663$).

Changes in liver volume and relief of symptoms

The data of the groups who received treatment (i.e. LAN 90 mg and LAN 120 mg; $n = 102$) were analysed. Improvement of complaints was assessed at 6 months at the moment that both patient and investigator were not aware of the results of the volumetry as mentioned before. Patients were systematically asked whether symptoms aggravated/stayed similar; or improved under treatment. This information was compared with the changes in LV at 6 months. Based on ROC analysis, a reduction of at least 120 mL in LV has a positive and negative predictive value of respectively 64% and 77% (ROC analysis AUC: 0.729; sensitivity 73%, specificity 69%, $P < 0.0001$) (Figure 4). In the LAN 90 mg group, 45% (23/51) of the patients reported to have fewer complaints. In the LAN 120 mg, 41% (21/51) of the patients had fewer complaints, of which eight patients were originally blinded for the treatment (LOCKCYST I) and 13 patients who crossed over from placebo to LAN 120 mg in the extension study (Fisher's exact test, $P = 0.09$).

Predictors of reduction in LV

Univariate analysis of the LAN 90 mg and LAN 120 mg group ($n = 102$) revealed only a positive correlation between LV baseline and the reduction in LV at 6 months (Pearson R: 0.389, $P < 0.0001$). The probability to induce a reduction of >120 mL after 6 months of treatment in function of baseline LV and LAN dose is presented in Figure 5. Our model shows that patients with larger LV's are expected to benefit more from treatment. Although the data suggest that LAN 120 mg is more beneficial than LAN 90 mg for each LV at baseline, there was no statistically significant difference

Table 1 | Baseline characteristics of the study population (n = 132)

	Placebo n = 26	LAN 90 mg n = 55	LAN 120 mg§ n = 51	P-value
Age, years‡	48 (43–53)	51 (47–57)	49 (44–54)	NS*
Gender (female/men)	22/4	50/5	44/7	NS†
Centre (Leuven/Nijmegen/ UCL)	12/14/0	42/0/13	24/27/0	
ADPKD/ADPCLD	21/5	43/8	31/20	0.02†
BMI (kg/m²‡)	25.0 (22.2–27.5)	24.6 (22.7–27.9)	25.7 (22.6–28.6)	NS*
Baseline LV, mL‡	4875 (3340–5630)	4992 (3871–7216)	4666 (2972–6199.9)	NS*
Clearance‡ mL/min/1.73 m² (ADPKD only; n = 92)	65.1 (40–87)	55.8 (37–71)	69.4 (51–89)	NS*

ADPKD, autosomal dominant polycystic kidney disease; ADPCLD, autosomal dominant polycystic liver disease; BMI, body mass index; LV, liver volume; LAN, lanreotide.

* Kruskal-Wallis ANOVA on RANKS.

† Chi-square.

‡ Data shown as median (IQR).

§ Twenty-four patients received previously placebo.

Table 2 | Side effects in the three groups (n = 132). A less clinically, however, not statistically significant, pronounced side effect profile can be observed in the group LAN 90 mg compared to LAN 120 mg

	Placebo n = 26	LAN 90 mg n = 55	LAN 120 mg n = 51	P-value* comparing LAN 90 mg and LAN 120 mg
Diarrhoea n (%)				
Mild	3 (12%)	30 (55%)	32 (63%)	NS
Steathorrhea	0	3 (5%)	8 (16%)	NS
Pale stool n (%)	0	16 (29%)	23 (45%)	NS
Abdominal cramps n (%)				
Mild	0	20 (36%)	26 (51%)	NS
Severe	0	1	0	NS
Flatulence	0	9 (16%)	3 (6%)	NS
Constipation n (%)	0	0	4 (8%)	NS
Hair loss n (%)	0	1	0	NS

LAN, lanreotide.

* Chi-square test.

between the two dose groups in predicted probability for a response >120 mL.

Changes in kidney volume and renal function from baseline to 6 months

For the analysis of KV, we excluded individuals with no renal disease: ADPCLD (n = 33) and renal transplant recipients (n = 2) and patients that underwent a nephrectomy (n = 1). In four patients, no paired data of KV were available. The KV at baseline, change in KV and the relative change in KV of the remaining 88 patients is given in Table 3. The reduction in kidney volume induced by LAN 120 mg was significantly different as compared to placebo. For the analysis of GFR, we had 92 paired observations. Changes in GFR (MDRD, mL/min/1.73 m²) in the three groups are respectively: −2 [(−5.4)–(+3)] in the placebo group; −2.8 [(−6.8)–(−0.3)] in the LAN 90 mg group and −0.24 [(−5.1–(+6.4)] in the LAN 120 mg group (Kruskal-Wallis One Way ANOVA on Ranks; P = 0.25). Kidney function was also estimated by means of CKD-EPI formula, as the latter has been described to be more accurate in estimating GFR >60 mL/min.[15] Comparison between the three groups did not result in statistically significant differences (ANOVA on Ranks, P = 0.129) (Table 4). More details about the renal function in the three groups are given in Table 4.

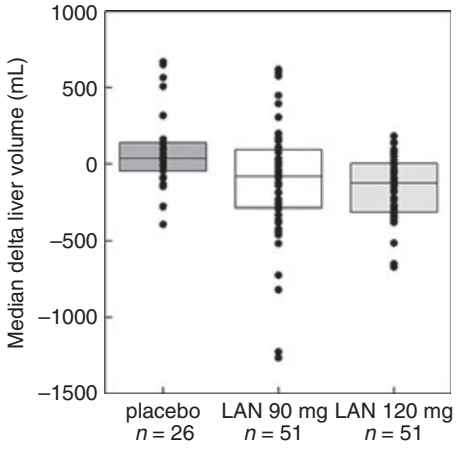

Figure 3 | Box plot analysis of the median changes in liver volume (LV) after 6 months (delta LV) in the three groups. Placebo group: increase of +36 mL [(−45)–(+138)]; LAN 90 mg group: decrease of −82 mL [(−285)–(+92)]; LAN 120 mg group: decrease of −123 mL [(−312)–(+4)] (Kruskal-Wallis One Way ANOVA on Ranks; $P = 0.002$).

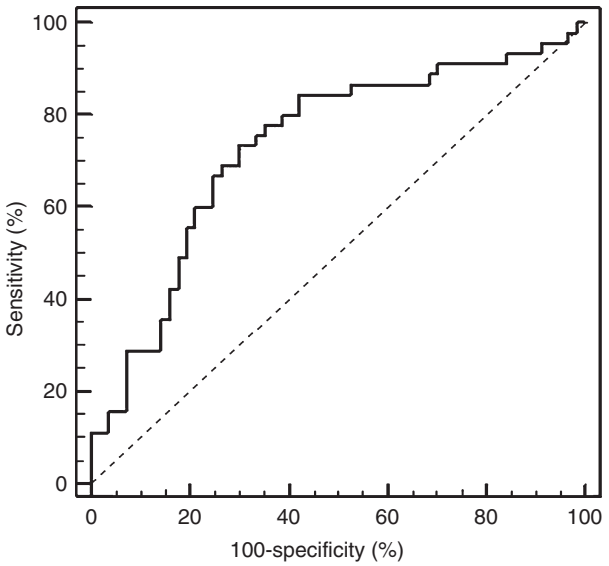

Figure 4 | ROC analysis of changes in liver volume (LV) and relief of symptoms in treated groups ($n = 102$). Patients were divided into three groups: clinical nonresponder (worse symptoms or no change) and clinical responder (less symptoms). This information was compared with the calculated changes in LV at 6 months. A reduction of at least 120 mL in LV has a positive predictive value of 64% for improving symptoms (AUC: 0.729; $P < 0.0001$).

DISCUSSION

The main observation of this study is that both LAN 90 mg and LAN 120 mg decrease LV after 6 months. This effect is numerical more pronounced when the highest LAN dose is used. In addition, the probability model shows that patients with larger LV's are expected to benefit more from treatment. Although the data suggest that LAN 120 mg is more beneficial than LAN 90 mg for each LV at baseline, there was no statistically significant difference between the two dose groups. It is possible that there is no difference between both doses in the effect on LV or that the difference is rather small and not detectable with the actual sample sizes due to lack of statistical power. Side effects were less pronounced in the group with the lower LAN dose, although not statistically significant from the higher dose group. This study, however, suggests that in case of

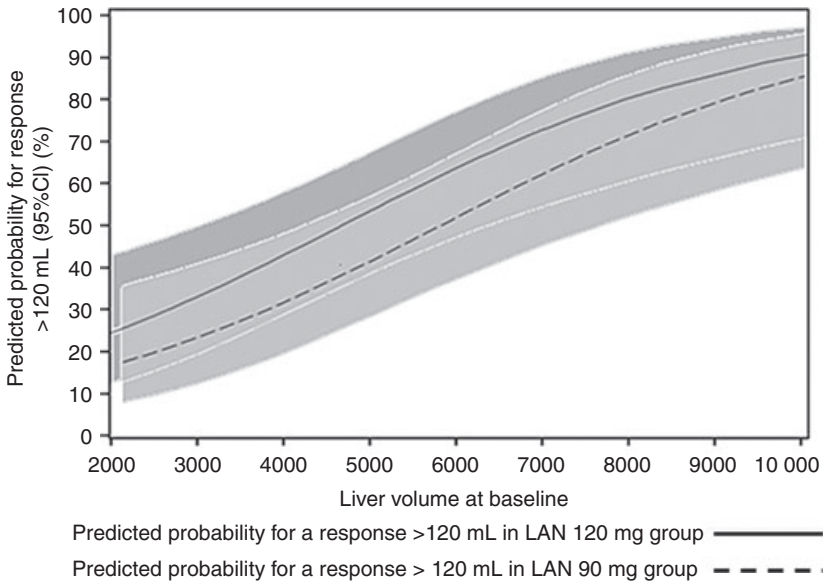

Figure 5 | Graph showing the probability to induce a reduction in LV >120 mL after 6 months of treatment in function of baseline liver volume (LV) and LAN dose. Patients with larger LVs are expected to benefit more from treatment. The data suggest that LAN 120 mg is more beneficial than LAN 90 mg for each LV at baseline, but there was no statistically significant difference between the two dose groups.

Table 3 | Changes in kidney volume after 6 months in the three groups (n = 88). The reduction in kidney volume induced by LAN 120 mg was significant compared to placebo

	Placebo n = 18	LAN 90 mg n = 41	LAN 120 mg n = 29	P-value*
Age (years)†	49(44–54)	51 (46–55)	49 (45–55)	NS
Kidney volume baseline (mL)†	927 (411–1874)	1255 (640–1902)	852 (494–1495)	NS
Change in kidney volume (mL)†	+25 (11–70)	−1.15 (−28–63)	−16.2 (−50–12)	0.003
Relative change in kidney volume (%)†	+3.1 (1.1–5.2)	−0.1 (−2–4.8)	−2.8 (−5.3–1.5)	<0.001

* Kruskal-Wallis ANOVA on RANKS.

† Data shown as median (IQR).

Table 4 | Data of the renal function in the three groups (n = 92). There were no statistically significant differences regarding change in kidney function between the three groups

	Placebo n = 21	LAN 90 mg n = 41	LAN 120 mg n = 30	P-value*
Creatinine baseline	0.9 (0.75–1.43)	1.06 (0.9–1.54)	0.89 (0.71–1.17)	NS
Creatinine 6 months	0.9 (0.75–1.38)	1.14 (0.94–1.61)	0.89 (0.74–1.12)	0.01
Clearance baseline MDRD	65 (40.1–87)	55.75 (37.3–70.5)	69.41 (50.8–88.7)	NS
Clearance 6 months MDRD	67.8 (47.2–90)	50.5 (36.8–64.6)	70.02 (50.89–85)	0.006
Change clearance 6 months MDRD	−2.1 (−5.4–3.1)	−2.8 (−6.8–(−0.3))	−0.24 (−5.05–6.38)	NS
Clearance baseline CKD-EPI	76 (44–100)	63 (41.75–76.25)	79 (54.25–100.75)	NS
Clearance 6 months CKD-EPI	79 (50.5–102.5)	57 (40–72)	80.5 (57–99)	0.008
Change clearance 6 months CKD-EPI	−2 (−6–3)	−3 (−8–(−1))	−1 (−5–4)	NS

* Kruskal-Wallis ANOVA on RANKS.

Data shown as median (IQR).

intolerance to a dose of 120 mg, it is meaningful to reduce the dose to 90 mg, which has still a beneficial effect compared to placebo.

Several studies have reported the beneficial effects of the somatostatin analogues: lanreotide (LAN) and octreotide LAR (octLAR) in decreasing liver and kidney growth in PCLD over a treatment period of 6 months, 12 months and 2 years.[9–12, 16] Interruption of somatostatin analogue treatment results in a rebound growth of cysts, LV, KV and hereby recurrence of clinical symptoms.[17] This suggests that this therapy should be considered as a long-term treatment during many years or as a bridge to more invasive therapy such as liver transplantation. In all these studies, the highest commercial available dose was used. However, some of these patients developed severe steatorrhea, with the need of pancreatic enzyme replacement therapy or even need discontinuation of the therapy. Preclinical studies in the PCK rat with octreotide suggested a dose-dependent effect on the liver and kidneys.[8] The optimal dose in humans has never been explored. Symptomatic PCLD is infrequent and our power calculation demonstrated that a prospective randomised dose range trial is unrealistic. Therefore, we pooled our data with LAN from three trials and all individual data were blindly re-analysed in a nonpaired way.

To evaluate in an objective way the therapeutic effect of LAN, it is of upmost importance to have accurate methods that are able to evaluate changes in LV over time. In this regard, we observed in this study an excellent reproducibility (by Pearson's correlation) and very good agreement (by Bland-Altman plots) between the two blinded radiologists and between the two software programs, which make these measurements suitable for broad clinical use.

Until now, it was never been investigated which reduction in LV was required to obtain an improvement of symptoms. In addition, to date, there is no standard validated questionnaire in PCLD to score the symptoms of these patients. Therefore, symptoms and complaints of which we interpreted them to be PCLD were noted at baseline. At month 6, at the moment that both patient and investigator were not aware of the results of the volumetry, systematically whether symptoms in general aggravated, remained stable or improved and we correlated this with the changes in LV. The proportion of patients experiencing less symptoms after 6 months with a LV reduction of ≥120 mL was 64% (negative predictive value: 77%).

This reduction of 120 mL lies above the 95% upper limit of the confidence intervals of the differences in LV assessed by the two methods as described above.

We also found a decline in KV with LAN. In the placebo group, KV increased with 3%, which is in line with previous reports.[9–12] We could not observe a beneficial effect on GFR. Possible reasons for not observing a beneficial effect on GFR may be among others: the relatively short duration of the observation (6 months), the fact that somatostatin induces renal vasoconstriction causing a reduction in renal blood flow and GFR and the nonlinearity of GFR decline in ADPKD.[18, 19]

Hogan *et al.* used in there trial OctLAR 40 mg, whilst in our trials, we used LAN 90 mg and LAN 120 mg. A dose of OctLAR 30 mg equals a dose of LAN 120 mg; however, the somatostatin receptor (SSTR) profile of both drugs is slightly different.[20] OctLAR is known to have slight higher affinity for SSTR2, SSTR3 and SSTR5 but a lower affinity for SSTR1 and 4 compared to LAN.[21] To date, we do not exactly know what the SSTR spectrum is in ADPKD and ADPCLD patients, and how their expression is different from normal hepatic and renal epithelia. The beneficial effect of a more potent SS- analogue which is known to have high affinity for 4 of the 5 SSTRs subtypes (SOM230, Novartis Pharma, Basel, Switzerland) is currently being investigated (NCT01670110).

This study has several limitations. This is not a randomised trial, the reasons why have been explained previously. In this study, we also counted 24 patients two times: at the moment they received placebo and later on when they received LAN 120 mg. However, all CT-scans were blindly re-analysed in a nonpaired way. Baseline characteristics (age, body weight and renal function) were systematically adjusted to the treatment episode.

In conclusion, this study confirms the positive effects of somatostatin analogues in reducing LV. A reduction of ≥120 mL in LV improves the symptoms in the majority of the patients. In case of intolerance to LAN 120 mg, a reduction to LAN 90 mg might have less side effects and is still effective compared to placebo.

AUTHORSHIP

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