



Published in final edited form as:

Liver Int. 2016 April ; 36(4): 595–602. doi:10.1111/liv.12986.

Alkaline phosphatase predicts response in polycystic liver disease during somatostatin analogue therapy: a pooled analysis

Tom J.G. Gevers¹, Frederik Nevens², Vicente E. Torres³, Marie C. Hogan³, and Joost P.H. Drenth¹

¹Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands ²Department of Gastroenterology and Hepatology, Gasthuis Leuven, Leuven, Belgium ³Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Abstract

Background & Aims—Somatostatin analogues reduce liver volumes in polycystic liver disease. However, patients show considerable variability in treatment responses. 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 four trials that evaluated long-acting somatostatin analogues (120 mg lanreotide or 40 mg octreotide) for 6–12 months in polycystic liver disease patients. We performed uni- and multivariate linear regression analysis with preselected patient, disease and drug variables to identify independent predictors of response, defined as per cent change in liver or kidney volume (in ADPKD subgroup). All analyses were adjusted for baseline liver volume and centre.

Results—We included 153 polycystic liver disease patients (86% female, median liver volume 4974 ml) from three international centres, 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 predicted liver volume reduction (-3.2% , $P = 0.03$) but did not predict kidney volume reduction ($+0.1\%$, $P = 0.97$). Total gastro-intestinal symptom severity decreased with therapy in a subgroup analysis ($n = 95$; $P < 0.001$).

Correspondence: Joost P.H. Drenth, MD PhD, Professor of Molecular Gastroenterology and Hepatology, Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, code 455, 6500 HB Nijmegen, the Netherlands, Tel: +31 24 3619190; Fax: +31 24 3540103, joostphdrenth@cs.com.

Supporting information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1111/liv.12986/supinfo

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

Keywords

ADPKD; ADPLD; alkaline phosphatase; drug therapy; hepatic cyst; somatostatin

Polycystic liver disease (PLD) is common in patients with autosomal dominant polycystic liver disease (ADPLD) (1, 2) and autosomal dominant polycystic kidney disease (ADPKD) (3). The progressive liver enlargement causes chronic symptoms and reduced quality of life (4). Somatostatin analogues (SAs), including lanreotide and octreotide, are thought to reduce polycystic liver volume by inhibiting cyclic adenosine monophosphate (cAMP) (5, 6). Recently, pooled analyses showed that treatment with SAs decreased polycystic liver volume in PLD patients when compared to placebo (7), and that the health-related quality of life improves with SA therapy (8). These findings suggest that polycystic liver growth can be suppressed by SAs.

While the overall majority of PLD patients show liver volume reduction with SA therapy, there is great inter-individual variability which makes it difficult to predict which patients will respond favourably. This can be because of patient-related factors, as it is suggested that PLD patients with larger polycystic livers had higher reductions in liver volume with lanreotide therapy (9, 10). Likewise, pharmacokinetic factors such as body weight, body mass index (BMI) or renal function may influence pharmacokinetic properties of SA (11). Finally, liver enzymes including alkaline phosphatase (ALP), gamma-glutamyl transferase and bilirubin are frequently elevated in PLD patients and might be associated with disease progression and treatment response (12, 13).

In this regard, 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 treatment strategy, preventing unnecessary and ineffective SA therapy in patients without response. In addition, identifying predictors of response will provide more insight in pathophysiology of liver volume progression in PLD. Unfortunately, the small number of patients from individual studies complicates the analysis of predictors. In this regard, we 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 investigated which patient, disease and treatment factors are independently associated with response in PLD patients, and explored the relationship between these factors and liver volume progression during SA therapy.

Patients and methods

Population

We included the individual patient (IPD) data from four trials (LOCKCYST, Mayo Clinic, ELATE, RESOLVE trial and extensions) that described the effect of long-acting SA (120 mg lanreotide (Somatuline Autogel; Ipsen, Boulogne Billancourt, France) or 40 mg octreotide (Sandostatin LAR; Novartis Pharma, Basel Switzerland)) for 6 or 12 months in adult PLD

patients and had change in liver volume as the primary outcome (see supplementary methods) (10, 14–17).

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 (The committee human research region Arnhem-Nijmegen (CMO Arnhem-Nijmegen) and Mayo Clinic Institutional Review Board), and all patients who participated in the studies provided written consent.

Data acquisition

We sent an electronic form containing data fields to be completed for individual patients to all principal investigators of included trials. The primary author (T.G) pooled all data, checked databases for completeness and internal consistency and made corrections through correspondence with investigators. We included PLD patients with ADPKD or ADPLD as the underlying disease and received SA therapy for >3 months. We collected liver volumes, kidney volumes and total gastro-intestinal symptom severity scores (measured by standardized gastro-intestinal symptom questionnaire) (19) at baseline and end of therapy. We obtained the following candidate predictors at baseline: sex, age, diagnosis, weight, BMI, 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. As oestrogen use and hormone replacement therapies were exclusion criteria in the original trials, we could not include this variable in our analysis. In case the patient participated in multiple trials, only the first trial period was included in the analysis. Patients that underwent invasive therapy during the treatment period or had sepsis at baseline were excluded.

Primary outcome

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, protocols and reproducibility are described elsewhere (10, 16, 20). All CT and MRI scans were blinded to patient identity, date of birth and date of scan. 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

Secondary outcomes were change in kidney volume and change in symptom severity (21) measured on the same time-points as the primary outcome. We used a standardized questionnaire to assess the presence and severity of 11 gastro-intestinal symptoms over the past 4 weeks using a seven-point Likert scale. Included symptoms were: lower and upper abdominal pain, heartburn, regurgitation, nausea, vomiting, loss of appetite and early satiety. Three PLD-specific questions were added: shortness of breath, increasing abdominal volume and involuntary weight loss. We used the total score of the questionnaire and the scores of the individual symptoms in our study.

The adjusted Ravine criteria were used to diagnose ADPKD; if patients did not fulfil the criteria, they were diagnosed as ADPLD (22). We categorized the population according to presence of severe hepatomegaly (yes vs no) by using the median baseline liver volume as a cut-off. We dichotomized weight to < 75 kg and BMI to < 26 , both by using the mean as a cut-off. Estimated GFR was assessed by using the four-variable MDRD formula, stratified as both continuous and dichotomized to < 60 or ≥ 60 ml/min/1.73 m² (23). ALP, gamma-glutamyl transferase and bilirubin were dichotomized to either elevated or normal. We used a cut-off for normal serum gamma-glutamyl transferase of < 35 U/L and < 45 U/L in women and men respectively, whereas a threshold of < 17 μ /mol was used for normal serum levels of bilirubin. As different cut-offs were used for normal ALP serum levels in laboratories, we compared ALP levels to the upper limit of normal (ULN) for that specific laboratory and calculated as a ratio. ALP was considered to be elevated if levels at baseline were ratio of > 1 and considered to be normal if the values had a ratio of ≤ 1 .

Statistical analysis

The IPD pooled analysis was conducted according to intention-to-treat principle. As liver volumes have a skewed distribution, we first calculated the logarithms of liver volumes and then carried out analyses. Effect estimates were backwards transformed and 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 primary outcome liver volume. Variables with $P < 0.2$ in univariate analysis were selected for multivariate analysis. We used backward selection to exclude variables in multivariate analysis, variables with a P -value of 0.05 retained in the model. We included the variable “centre” as a random effect in all analyses to take into account the heterogeneity among different centres. In addition, we adjusted for baseline liver volume in all analyses.

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 it was associated with response to therapy.

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. Finally, we calculated changes in total and individual symptom severity scores after somatostatin analogue therapy, using the Wilcoxon signed-rank test and paired t -test respectively.

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 version 20.0 (SPSS Inc., Chicago, IL) by TG. All P -values calculated were two-tailed, and the level of significance was set at $\alpha = 0.05$.

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 153 of a total of 183 trial episodes for our study; 28 episodes were excluded due to participation of patients in multiple trials and two episodes were excluded because patients were on placebo while participating. The general characteristics of 153 patients are reported in Table 1. Overall, most patients had moderate to severe PLD, were female (86%) and received SA therapy for 12 months. The majority of patients had ADPKD (69%). 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 ADPLD ($n = 48$), renal transplantation ($n = 4$) or incomplete image coverage of kidneys ($n = 1$). No patient underwent liver surgery, liver transplantation or percutaneous interventional therapy during the trial.

Primary outcome – change in liver volume

Median liver volume decreased from 4974 to 4787 ml in this study population ($n = 153$) after 6–12 months, resulting in a mean change in liver volume of -4.2% . Responses in individuals ranged from -31.7 to $+9.5\%$.

Baseline age, weight, BMI, sex, presence of severe hepatomegaly, SA type, eGFR and bilirubin status (elevated vs normal) did not affect response during SA therapy in the univariate analysis (Table 2). Both diagnosis (ADPLD 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 significantly predicted 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 (-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 with therapy, and 3.3% (95% CI 4.5 to 7.7%) in patients with normal ALP (Fig. 1). As baseline liver volume possibly impacted the association between baseline ALP status and change in liver volume, we also checked for interaction, which was absent ($P = 0.58$).

Treatment duration (12 vs 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. In addition, everolimus co-therapy did not affect responses during SA therapy ($P = 0.47$).

As elevated alkaline phosphatase is associated with renal osteodystrophy in patients with chronic renal failure, we excluded all patients that had kidney transplantation or had an $\text{eGFR} < 30 \text{ ml/min/1.73 m}^2$ ($n = 11$) 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 liver volume response in the remaining 111 PLD patients. Elevated gamma-glutamyl transferase at baseline did not significantly increase liver volume response (-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 kidney volume analysis, corresponding with a change of -0.6% (range -15.6 to $+22.5\%$). 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% vs -0.7% ; Fig. 2A), whereas elevated ALP status was still associated with increased reduction in liver volume (-6.3% vs -3.0% ; Fig. 2B).

Secondary outcome – change in symptoms severity

We performed a subgroup analysis in 95 patients who completed the gastro-intestinal symptom questionnaire (the Mayo Clinic trial did not include the questionnaire). Median total symptom severity decreased from 19.7 (interquartile range (IQR) 12.1–31.7) to 15.2 (IQR 7.6–24.2; $P < 0.001$). The following individual symptom scores improved with therapy: nausea ($P = 0.04$), heartburn ($P < 0.01$), regurgitation ($P < 0.01$), early satiety ($P < 0.01$) and abdominal distension ($P < 0.001$; Supplementary Table 1). Higher total symptom scores at start were associated with larger decreases in symptom severity ($P < 0.001$ with Spearman correlation coefficient) with SA therapy.

Probability for good response

We checked whether ALP status also affected probability of achieving a good response, defined by using different cut-offs for reduction in liver volume (Supplementary Figure 1). Probability of achieving a good response decreased 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, and 31% for patients with normal ALP.

Discussion

Main finding of our study was that baseline elevated ALP predicted increased liver volume reduction in PLD patients during SA therapy, whereas it was not associated with 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 unknown there is evidence to suggest that ALP affects the secretory function of cholangiocytes. The apical membrane of cholangiocytes is 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 (24). As such, ALP counter regulates secretory stimulation of cholangiocytes preventing further increases in bile pressure during obstructive cholestasis (24).

ALP could exert a similar role in PLD, counteracting fluid secretion from cholangiocytes lining hepatic cysts, and enhance the effect of SAs on cAMP-dependent fluid secretion (25, 26). The conjecture is that elevated ALP plays a protective role in PLD. This would also explain the discordant effect of ALP on polycystic livers and kidneys observed in our study. The inhibitory effects of ALP on ductular cholestasis have recently been emphasized (27). Cytotoxic bile acids are major determinants of ALP activity. Indeed, there are increased concentrations of cytotoxic bile acids in the liver of an animal model of PLD (PCK rat) compared to normal controls, and in the cystic fluid of PLD patients compared to their paired serum samples (28). In addition, the bile acid glycodeoxycholic acid stimulated the proliferation of human polycystic cholangiocytes. Ursodeoxycholic acid (UDCA) was able to halt progression of liver volume in rats through decreasing intrahepatic accumulation of cytotoxic bile acids and decreasing cholangiocyte hyperproliferation. Collectively, these data support a role of bile acids and ALP in the aetiology and pathogenesis of PLD, and provide a hypothesis to favour use of UDCA as a potential treatment to target hepatic cystogenesis in PLD patients (28).

Several studies found elevated ALP levels in PLD patients (15–47%), similar to the proportion (31%) observed in our study (13, 29–31). Patients with elevated ALP were more likely to have an indication for liver transplantation (13) or to have invasive treatment in these retrospective studies, which suggested a worse prognosis instead of the improvement in liver volume we observed in our study (30). 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 <3 L (25th percentile) had elevated ALP at baseline. This contrasts to 60% in patients with a baseline liver of >7 L (75th percentile). It is therefore likely that in these retrospective studies the need for therapy was triggered by the severity of hepatomegaly rather than the elevated ALP. Our study clearly shows that elevated ALP predicted liver volume response during SA therapy independently of baseline liver volume.

We found that total gastro-intestinal symptom severity decreased with SA therapy, underlining the efficacy of SA therapy in PLD. Unfortunately, we could not investigate quality of life outcomes because different questionnaires were used in the included trials. Recently, a PLD-specific questionnaire was developed that was more sensitive to change in PLD related symptoms than the generic gastro-intestinal questionnaire used in this study (32). This validated questionnaire can be used in future studies to investigate whether our findings also affect clinical responses.

The failure to detect a significant effect of gamma-glutamyl transferase on liver volume response can be due to the low number of patients included in this analysis. It is therefore too early to exclude gamma-glutamyl transferase as a potential predictor of liver volume response. Larger cohort studies are necessary to properly investigate the role of gamma-glutamyl transferase in PLD.

Both presence of severe hepatomegaly and SA compound (octreotide or lanreotide) were not associated with change in response in our study. This is in line with results of a recent meta-analysis that compared the effect of SA with placebo in PLD patients (7).

Our results indicate that elevated ALP can serve as a liver-specific biomarker for volume response in patients requiring SA treatment. At the moment, SAs are used off-label or in the context of clinical trials to highly symptomatic patients unfit for or unwilling to undergo surgical therapies (33). Given the high costs of SAs, it would be preferable to initiate treatment in those patients with high probability for achieving a response. 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 beyond 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 candidates for therapy given their symptoms of severity of PLD were from different international centres, which increases generalizability of our findings. However, if clinicians want to replicate these results in clinical practice, they should follow inclusion criteria used in included RCTs.

A limitation of 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. Second, although we included the largest group to date of SA-treated patients with severe PLD, the total study population remains limited. This reduced the number of independent variables we could investigate for our study. Finally, 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 (34). However, elevated ALP remained a significant predictor for response when ADPKD patients at high risk for renal osteodystrophy (eGFR < 30 ml/min/1.73 m² 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, 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.

Acknowledgments

We thank Angela Ihrke and Melissa Chrispijn for collecting the original trial data.

Financial support: T.J.G. Gevers was sponsored by the EASL Andrew K. Burroughs Short Term Fellowship Programme. Frederik Nevens has received previous grant support from Ipsen. Vicente E. Torres has participated in an expert panel meeting sponsored by Ipsen Innovation to discuss the potential of lanreotide in the treatment of patients with PLD. Marie C. Hogan has received previous funding support from Novartis USA. Joost P. H. Drenth has received previous grant support from Ipsen and Novartis. The costs of this study were borne by the authors' institutions.

Conflicts of Interest: The authors do not have any disclosures to report.

Abbreviations

ADPKD	autosomal dominant polycystic kidney disease
ADPLD	autosomal dominant polycystic liver disease
ALP	alkaline phosphatase
BMI	Body mass index
cAMP	cyclic adenosine monophosphate
CI	confidence interval
eGFR	estimated glomerular filtration rate
IPD	individual patient data
IQR	interquartile range
PLD	polycystic liver disease
SA	somatostatin analogue
UDCA	ursodeoxycholic acid
ULN	upper limit of normal

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Key Points

- Elevated alkaline phosphatase predicts liver volume response in polycystic liver disease patients during somatostatin analogue therapy.
- Somatostatin analogue type, underlying diagnosis and baseline renal function do not affect liver volume response during somatostatin analogue therapy.
- Gastro-intestinal symptom severity decreases with somatostatin analogues therapy.
- Alkaline phosphatase could serve as a liver-specific biomarker for response in polycystic liver disease patients requiring somatostatin analogue treatment.

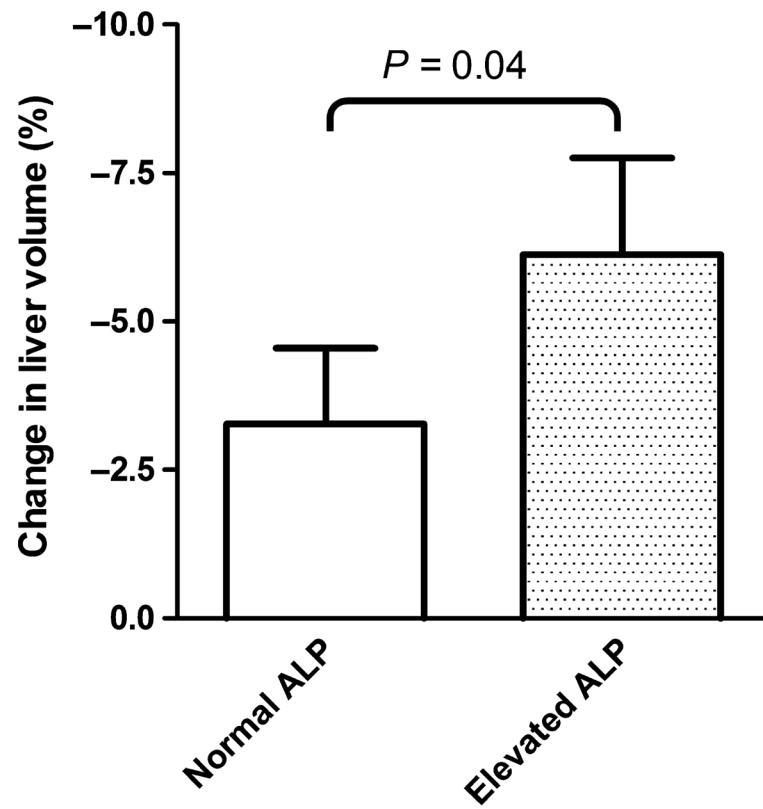


Fig. 1.

Liver volume reduction according to ALP status. Per cent changes in liver volume in 153 PLD patients with normal ($n = 105$) and elevated ALP ($n = 48$) at baseline. Data are shown in mean and 95% CI.

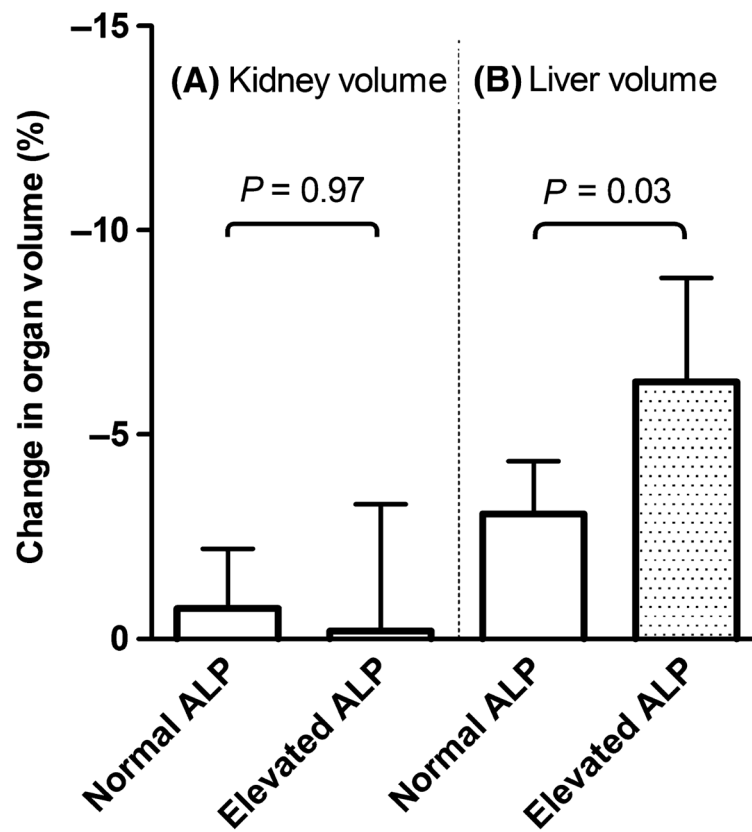


Fig. 2.

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 are shown in mean and 95% CI.

Table 1Baseline characteristics of patients ($n = 153$)

Trial, n (%)	
LOCKCYST + extension (10, 14)	51 (33)
MAYO + extension (15, 16)	42 (28)
ELATE (17)	32 (21)
RESOLVE (18)	28 (18)
Centre, n (%)	
Radboudumc, Nijmegen, Netherlands	87 (57)
University Hospital Leuven, Belgium	24 (16)
Mayo Clinic, Rochester, Minnesota, USA	42 (28)
Age, y, mean (range)	50 (32–70)
Weight, mean (range)	75 (50–130)
BMI, mean (range)	26 (18–41)
Diagnosis (ADPKD/ADPLD)	105/48
Sex (male/female)	21/132
Liver volume, ml, median (range)	4974 (1300–15 320)
Kidney volume, ml, median (range)*	945 (267–4566)
Compound (octreotide/lanreotide)	70/83
Everolimus co-therapy (yes/no)	10/143
Duration of SA therapy (6 months/12 months)	43/110
Kidney transplantation (yes/no)	4/148
eGFR, ml/min/1.73 m ² , mean (range)	70 (19–124)
ALP times normal, median (range)	0.8 (0.4–5.7)
ALP (elevated/normal) [†]	48/104
Bilirubin, $\mu\text{mol/L}$, median (range)	10 (5–33)
Bilirubin (elevated/normal) [‡]	12/141
Gamma-glutamyl transferase, U/L, median (range) [§]	78 (17–555)
Gamma-glutamyl transferase (elevated/normal) [¶]	85/26

* Only ADPKD patients.

[†] Cut-off for normal was a ALP value with a ratio of 1 compared to the upper limit of normal.[‡] Cut-off for normal was 17 $\mu\text{mol/L}$.[§] Included the 111 patients with measured gamma-glutamyl transferase at baseline.[¶] Cut-off for normal was <35 U/L in women and <45 U/L in men.

Table 2

Univariate and multivariate analysis using liver volume as the dependent variable

Variable	Univariate * % change (95% CI)	P-value	Multivariate * % change (95% CI)	P-value
Age (y), continuous	0.0 (−0.1 to 0.2)	0.60		
Sex (male/female)	1.8 (−1.4 to 5.1)	0.27		
Diagnosis (ADPLD/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		
BMI, continuous	0.0 (−0.3 to 0.3)	0.84		
BMI, or < 26	0.2 (−2.1 to 2.5)	0.88		
Severe hepatomegaly (yes/no) [‡]	−1.0 (−4.8 to 3.0)	0.62		
Compound (octreotide/lanreotide)	−1.2 (−4.0 to 1.6)	0.39		
eGFR (ml/min/1.73 m ²), continuous	0.0 (−0.1 to 0.0)	0.32		
eGFR (ml/min/1.73 m ²), or <60	1.2 (−1.2 to 3.7)	0.34		
ALP (elevated/normal) [‡]	−2.7 (−5.1 to −0.2)	0.04	−2.7 (−5.1 to −0.2)	0.04
Bilirubin (elevated/normal) [§]	2.6 (−1.6 to 6.9)	0.23		

Bold: variables selected for multivariate analysis.

* All analyses are adjusted for centre and baseline liver volume.

[‡]We used the median (4974 ml) as the cut-off value for presence of severe hepatomegaly.[‡]Cut-off for normal was a ALP value with a ratio of 1 compared to the upper limit of normal.[§]Cut-off for normal was 17 µmol/L.