Ursodeoxycholic acid in advanced polycystic liver disease: A phase 2 multicenter randomized controlled trial

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Introduction

Polycystic liver diseases (PLDs) are genetic disorders that lead to the formation of cysts throughout the liver [1]. PLD is present in a large proportion of patients with autosomal dominant polycystic kidney disease (ADPKD), a disorder where the majority of patients (94%) develop hepatic cysts in addition to kidney cysts [2]. Multiple hepatic cysts can also appear in patients without renal involvement (i.e., autosomal dominant polycystic liver disease [ADPLD]). Due to progressive cyst growth, patients can develop hepatomegaly. This could lead to symptoms such as abdominal pain, early satiety and an impaired health-related quality of life (HRQL) [1,3,4]. Current therapies for PLD such as fenestration and liver transplantation are invasive with high risk of complications [5]. Medical treatment with somatostatin analogues does hold some promise and is able to reach a total liver...
volume (TLV) reduction of ~5% in 6–12 months [6–8]. However, not all patients do respond and some may develop side effects such as glucose intolerance, diarrhea or gallstones. Moreover, somatostatin analogues are very expensive. Therefore, other options are needed.

The genetic profile of ADPKD and ADPLD is distinct but the resulting liver phenotype is similar [1]. ADPKD is mainly caused by mutations in the polycystic kidney disease 1 gene (PKD1) or PKD2 gene, while ~25% of ADPLD cases have a mutation in one of the three known genes PKRCSH, SEC63 or LRPS [9]. The PKD genes encode for polycystin 1 and 2 respectively, both integral membrane proteins acting as a Ca $^{2+}$ permeable receptor channel complex [10]. Mutations in polycystins result in decreased intracellular calcium levels (Ca $^{2+}$) and subsequent increased intracellular cyclic adenosine monophosphate (cAMP) levels [10,11]. This promotes the hyperproliferation of cystic cholangiocytes and is a crucial step in hepatic cyst formation that might serve as a potential target for novel pharmacological therapy [10–13]. In this regard, previous studies have shown that cholangiocytes from PCK rats, an animal model with PLD resembling [10,11], this beneficial effect of UDCA was also associated with downregulation of the high concentration of cytotoxic bile acids found in PCK rat livers [17]. UDCA is safe and well tolerated in the treatment of patients with primary biliary cholangitis and gallstone disease [18].

The hydrophilic bile acid, ursodeoxycholic acid (UDCA), is a well-known Ca $^{2+}$ agonist in hepatocytes [14] and cholangiocytes [15]. We recently demonstrated that UDCA restores diminished Ca $^{2+}$ levels in polycystic human cholangiocytes in culture and decreases hepatic cystogenesis in PKC rats after 5 months of treatment [16,17]. This beneficial effect of UDCA was also associated with downregulation of the high concentration of cytotoxic bile acids found in PCK rat livers [17]. UDCA is safe and well tolerated in the treatment of patients with primary biliary cholangitis and gallstone disease [18].

We hypothesized that 6 months of UDCA treatment leads to reduction in liver volume, symptoms and improvement of HRQL in PLD. Therefore, we designed an international, multicenter, randomized controlled phase 2 trial with proportional change in TLV as the primary endpoint.

Material and methods

Study population

We included symptomatic PLD patients between 18 and 80 years with an underlying diagnosis of ADPLD or ADPKD, and a TLV $>$ 2500 ml. PLD was defined as the presence of $>$ 20 liver cysts on computed tomography (CT) or magnetic resonance imaging (MIR) scan, and ADPKD diagnosis was based upon modified Ravine criteria [19]. Liver volume was judged by one of the investigators and based on clinical findings (symptoms and physical examination), imaging or former TLV assessments. Symptomatic PLD was defined as an Eastern cooperative oncology group – performance status of $>$ 1 and the appearance of at least three of the following symptoms: abdominal pain, abdominal distension, abdominal fullness, dyspnea, early satiety, back pain, nausea/vomiting, anorexia, weight loss and jaundice [20]. Full details of inclusion and exclusion criteria are shown in Supplementary materials and methods.

This trial was conducted at three university centers specialized in PLD: one in Spain (Donostia University Hospital, San Sebastián, Spain) and two in the Netherlands (Academic Medical Center Amsterdam and Radboud university medical center, Nijmegen).

Trial design and treatment allocation

Eligible patients were randomly assigned in blocks of four in a 1:1 ratio to receive UDCA (Ursocol, Zambon, the Netherlands), orally twice a day, in a dose of 15–20 mg/kg/day for 24 weeks, or to undergo follow-up without any clinical trial treatment. Sequence generation was handled by an independent researcher using www.randomization.com. To ensure allocation concealment, all randomization numbers were placed in opaque, sealed envelopes bundled per four. Envelopes were opened by an independent researcher one day before baseline in order to prepare medication. The independent researcher passed details of group allocation on to the clinical researcher of each center.

UDCA was provided by the local pharmacy of every center. Treatment was initiated the day after baseline visit. Compliance with medication was assessed at week 24 by pill count. During the trial, patients were not allowed to undergo interventions such as aspiration sclerotherapy or surgery, or to use somatostatin analogues.

Study procedures

A 36-week follow-up period was planned, in which a total of five visits at the outpatient clinic were scheduled: week 0 (baseline), 4, 12, 24 (end of treatment) and 36 (follow-up) (Fig. 1). For safety measures, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), bilirubin (direct and total), gamma-glutamyltransferase (GGT), alkaline phosphatase (AP), creatinine and international normalized ratio (screening only) were assessed during all visits and adverse events were recorded. At week 0 and 24 CT scans without contrast were performed on a multidetector CT scanner. CT scans had a slice thickness of 3 mm.

For analysis of the primary outcome, all CT scans were blinded to patient identity, treatment allocation and date of scan. Scans were measured in random order. TLV and total kidney volume (TKV) were calculated by 3D measurement of CT scan slices using Pinnacle$^{3}$ version 9.6 g (Phillips Healthcare in Fitchburg, WI, USA) [21]. Liver and kidneys were outlined manually every 9 mm. Software interpolated intermediate slices and calculated areas within the indicated circumference, and finally, TLV and TKV were determined. To test whether TLV measurements were reliable, a random set of 18 CT scans (9 baseline and 9 week 24) were measured by two researchers (HD & MN) and inter-observer variation was assessed using a Bland-Altman plot. Bland-Altman plot showed a mean difference of ~0.2 ± 2% between the two researchers. TLVs from one researcher (HD) were used for analysis of primary outcome.

Liver cyst volume (LCV) was measured blindly, by fully automatic segmentation of liver images using an image processing pipeline built in MeVisLab (version 2.7.1, MeVis Medical Solutions AG, Bremen, Germany) inspired by Ruggenenti [22]. Parameters for automatic segmentation were maintained constant for all patients to prevent variability between measurements. Images were initially smoothed by an anisotropic diffusion filter, using the modified curvature diffusion equation (time step 0.0625, conductance parameter 3, number of iterations 15) [23]. This filter reduces image noise without compromising edges or other important details in the image. Subsequently, images were marked with the LTV segmentation exported from Pinnacle (border voxelized at midpoint, in order to reproduce pinnacle TLV values), and Otsu thresholding (512 bins) was used for analysis of primary outcome.

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Fig. 1. Trial design of the CURSOR trial. Patients were screened for eligibility and eligible patients were randomized in an equal ratio to either the UDCA group or the control group. All patients received a CT scan at baseline and 24 weeks. Control visits were performed at week 4, 12 and 24 after baseline. A follow-up visit was performed 12 weeks after end of study (week 36).
performed to divide the liver into two classes [24]: cystic volume and parenchyma, based on the image histogram. TLV and LCV were calculated from these segmentations.

Endpoints

Primary outcome of this trial was proportional change in TLV from baseline to week 24 between UDCA group and control group. Secondary endpoints were: change from baseline to 24 weeks in (i) absolute and height-adjusted TLV (hTLV), (ii) absolute and height-adjusted total kidney volume (hTKV), (iii) symptoms, and (iv) HRQL. In addition, safety and tolerability were evaluated. Analysis of LCV as a secondary outcome parameter was added to the protocol after the trial had started in order to relate our findings to the results in PCK rats treated with UDCA [17].

Symptoms were assessed using the PLD questionnaire (PLD-Q) and gastrointestinal-questionnaire (GI-Q). The PLD-Q is a recently developed and validated questionnaire for PLD patients that includes 13 items about frequency and discomfort of PLD-specific symptoms such as early satiety and abdominal pain [25]. The GI-Q includes 11 items related to abdominal symptoms [26,27].

Generic HRQL was measured by the medical outcomes study 36-item short-form health survey (SF-36) and the European organization for research and treatment of cancer quality of life questionnaire core-30 (EORTC). The SF-36 consists of eight scales resulting in a norm-based summarizing physical (PCS) and mental component score (MCS). The EORTC is a validated questionnaire that includes nine symptom scales. Finally, we measured overall HRQL using the visual-analogue scale score of the European quality of life-5 dimension (VAS-EQ5D). Scoring manuals were used to calculate scores and to handle missing items.

Sample size and statistical analysis

A change in TLV of 4% in favor of UDCA compared to no treatment was assumed to be clinically relevant, based on previous trials with somatostatin analogues [28]. A priori sample size calculation revealed a sample size of minimum 34 patients for a statistical power of 80%, a type I error of 0.05 using a two-tailed test, a standard deviation of 4% and a dropout rate of 10%. Clinical outcome variables were analysed on a modified intention-to-treat basis defined as all randomly assigned patients. No interim analyses were done.

Continuous variables were expressed as mean (95% confidence interval (CI)) if normally distributed, otherwise as median (interquartile range (IQR)). Primary outcome and secondary outcomes on TLV, TKV, HRQL and symptoms were tested for missing outcomes in the analyses of primary and secondary endpoints. Adverse and serious adverse events were counted per group and patient. Most frequent adverse events and all serious adverse events were reported. A chi-squared test was used to compare numbers of episodes of adverse events between the control and UDCA group. In order to assess differences in response to UDCA, post-hoc subgroup analyses of ADPKD and ADPLD patients’ outcomes were performed for primary and secondary outcomes.

All p values calculated were two-tailed, and a p value <0.05 was considered statistically significant. Analyses were performed using SPSS 22.0 (SPSS Statistics, Inc., Chicago, IL, U.S.A.).

Ethical consideration and registration

Ethical approval for the two Dutch centers was obtained from the local institutional review board, i.e., the committee human research region Arnhem-Nijmegen (CMO Arnhem-Nijmegen). For the Spanish center, ethical approval was obtained from the ethics committee for clinical research (CEIC-Euskadi). The study was performed in accordance with the guidelines of Good Clinical Practice/ICH and the principles of the Declaration of Helsinki. Every patient signed informed consent. Safety of trial subjects was monitored by an independent data safety monitoring board. This trial is registered at [https://www.clinicaltrialsregister.eu/; EudraCT Number: 2013-003207-19] and at [https://www.clinicaltrials.gov; identifier: NCT02021110].

Results

Study population

From May 2014 through February 2015, 38 patients were screened for eligibility and 34 patients were randomized. A flow chart of the study population is shown in Fig. 2. All patients completed the total follow-up of 36 weeks by November 2015. Imaging analysis revealed that one patient (UDCA group) did not meet the inclusion criterion TLV ≥ 2500 ml; this patient was excluded from further analyses. Another patient was excluded from analysis of primary outcome only, as baseline CT scan was missing (UDCA group). In total 32 patients were analysed for primary outcome and 33 for secondary outcomes. Median age was 53 years [IQR: 42–58 years] in the UDCA group and 48 years [IQR: 43–53 years] in the control group (Table 1). In the control group 7 patients (40%) had ADPKD, compared to 9 patients (60%) in the UDCA group. Mean hTLV was 3207 ml/m (95% CI: 2627–3786 ml/m) and 3940 ml/m (95% CI: 2722–5157) ml/m in the control and UDCA group, respectively. Mean dose of UDCA in the intervention group was 19.9 ± 0.7 mg/kg/day. Compliance, assessed by the average number of pills taken, was 97.0 ± 3.0%. There were no dose reductions or drug discontinuations during the trial.

Liver volume

The proportional change in TLV from baseline to 24 weeks between both arms was not significantly different (UDCA group: 4.6% vs. control group: 3.1%; p = 0.493) (Fig. 3). Mean TLV increased from 6697 ml (95% CI: 4605–8788 ml) at baseline to 6954 ml (95% CI: 4781–9127 ml) at week 24 in the UDCA group, indicating a mean relative increase of 4.6% (95% CI: 0.3%–8.8%) (Table 2). TLV in the control group increased from 5512 ml (95% CI: 4445–6579 ml) to 5724 ml (95% CI: 4548–6900 ml), a mean relative increase of 3.1% (95% CI: 1.1%–5.1%). Individual changes in TLV for both groups showed that TLV decreased in 3 patients treated with UDCA and in 3 patients in the control arm (Fig. 4). One patient (UDCA group), diagnosed with ADPLD, had an extreme increase in TLV of 30%. A sensitivity analysis of
primary endpoint in which this patient was excluded, did not change results. There was no significant change in proportional TLV from baseline to week 24 between UDCA and control group in a subgroup analysis of ADPKD and ADPLD patients (respectively \( p = 0.267 \) and \( p = 0.210 \)).

In addition, there was no statistically significant difference in \( \text{hTLV} \) after 24 weeks between UDCA group (152 ml/m, 95% CI: 32–272 ml/m) and control group (121 ml/m 95% CI: 41–201 ml/m) (\( p = 0.642 \)). Notably, in a subgroup analysis of ADPKD patients, \( \text{hTLV} \) significantly increased in the control group (172 ml/m, 95% CI: 54–302, \( p = 0.018 \)) compared to a non-significant increase in the UDCA group (152 ml/m, 95% CI: –16–319, \( p = 0.071 \)) this increase was not statistically different between both groups (\( p = 0.835 \)). In ADPLD patients, \( \text{hTLV} \) did not change within and between UDCA and control group respectively (85 ml/m, 95% CI: –31–202 ml/m vs. 153 ml/m, 95% CI: –92–398 ml/m, \( p = 0.507 \)).

### Liver cyst volume

Mean LCV increased 376 ml (95% CI: 131–620 ml) in the control group compared to 342 ml (95% CI: 63–621 ml) in the UDCA group (\( p = 0.848 \)) (Table 2). Notably, subgroup analysis in ADPKD patients disclosed a significantly higher increase in LCV in the control group (470 ml, 95% CI: 100–840 ml) compared to the UDCA group (81 ml, 95% CI: –103–264 ml) (\( p = 0.049 \)). In contrast, in ADPLD patients there were no differences in LCV change between the UDCA and control group detected (473 ml, 95% CI: 63; 882 ml vs. 202 ml, 95% CI: –56; 461 ml, \( p = 0.296 \)).

### Kidney volume

Proportional change in TKV of ADPKD patients (\( n = 16 \)) from baseline to week 24 was not different between the UDCA and control group (0.5% vs. 0.6%, \( p = 0.858 \)). Interestingly, hTKV increased significantly from 897 ml/m (95% CI: 189–1605) to 917 ml/m (95% CI: 199–1635) in the control group (\( p = 0.044 \)) but not in the UDCA group (904 ml/m to 913 ml/m, \( p = 0.213 \)). Though, analysis between groups showed no statistical significant change (\( p = 0.335 \)) (Table 2).

### Symptoms and quality of life

EORTC score improved by 6 points in UDCA treated patients and worsened by 4 points in control group patients (\( p = 0.039 \)) (Supplementary Table 1). In a subgroup analysis of UDCA treated ADPKD patients, EORTC score improved by a mean decrease of 10 points (95% CI: –20.0, \( p = 0.047 \)) while score increased with 2 points in the control group (95% CI: –7;11, \( p = 0.628 \)). This improvement in the UDCA group tended to be larger than in the control group (\( p = 0.064 \)).

No significant symptom improvement was seen in PLD-Q and GI-Q symptom scores (respectively, \( p = 0.306 \) and \( p = 0.419 \)). Quality of life as measured by PCS and MCS score of SF-36 and VAS-EQ5D were not different from baseline to week 24 between control and UDCA group (respectively, \( p = 0.505 \), \( p = 0.819 \) and \( p = 0.255 \)).

### Safety endpoints: serum liver tests

No changes in biochemical tests were observed from baseline to week 24 between treatment arms, except for GGT (Supplementary Table 2). GGT significantly decreased in the UDCA group from 2.45 times upper limit of normal (ULN) (IQR: 1.18–4.71 times ULN) to 0.75 times ULN (IQR: 0.49–1.00 times ULN) and increased in the control group from 1.58 times ULN (IQR: 1.00–3.15 times ULN) to 1.85 times ULN (IQR: 0.97–3.49 times ULN) times ULN \( p < 0.001 \) between treatment groups). In addition, AP decreased in the UDCA group (\( p = 0.017 \)) but not in the control group (\( p = 0.277 \)). Though, change in AP was not statistically different between groups (\( p = 0.086 \)).

### Adverse events

Three patients were hospitalized during the trial: one patient (UDCA group) because of a brain contusion after falling down...
A total of 28 patients show an increase in TLV, while TLV decreases in 6 patients, 3 in the control and 3 in the UDCA group.

Table 2. Primary and secondary volumetry outcomes.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Control group (n = 17)</th>
<th>UDCA group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Week 24</td>
<td>p value*</td>
</tr>
<tr>
<td>Baseline</td>
<td>Week 24</td>
<td>p value*</td>
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<tr>
<td>TLV (ml)</td>
<td></td>
<td></td>
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<tr>
<td>Both 5512</td>
<td>5724</td>
<td>212 (70;354)</td>
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<tr>
<td></td>
<td>(4445;6579)</td>
<td>(4548;6900)</td>
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<td>ADPKD 6548</td>
<td>6845</td>
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<td></td>
<td>(4524;8571)</td>
<td>(4674;9016)</td>
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<tr>
<td>ADPLD 4787</td>
<td>4939</td>
<td>152 (-55;359)</td>
</tr>
<tr>
<td></td>
<td>(3519;6305)</td>
<td>(3516;6363)</td>
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<tr>
<td>hTLV (ml/m)</td>
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<td>121 (41;201)</td>
</tr>
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<td></td>
<td>(2622;3786)</td>
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<td></td>
<td>(2704;4908)</td>
<td>(2798;5158)</td>
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<tr>
<td>ADPLD 2787</td>
<td>2872</td>
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<td></td>
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<td>(2122;3622)</td>
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<tr>
<td>LCV (ml)</td>
<td>Both 3346</td>
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<tr>
<td></td>
<td>(2616;4076)</td>
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<td>ADPKD 3774</td>
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<td>(1122;11,104)</td>
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<tr>
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<tr>
<td>TKV (ml)</td>
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<td>hTKV (ml/m)</td>
<td>ADPKD 897</td>
<td>917 (199;1635)</td>
</tr>
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<td></td>
<td>(189;1605)</td>
<td>(0.7;39.5)</td>
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</tbody>
</table>

Data are reported as mean (95% CI). ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; hTKV, height-adjusted total kidney volume; hTLV, height-adjusted total liver volume; LCV, liver cyst volume; TKV, total kidney volume; TLV, total liver volume; UDCA, ursodeoxycholic acid.

*Comparison within groups (paired analyses), †comparison between groups (unpaired analyses).

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Discussion

The objective of this study was to evaluate the efficacy and safety of UDCA in patients with advanced PLD with an underlying disease of ADPKD or ADPLD. Our results indicate that UDCA treatment for 24 weeks did not reduce TLV in patients with advanced PLD. Proportional liver volume, hTLV and absolute liver volume were unaffected by UDCA in the whole treatment group and remained within margins seen in controls. However, post-hoc analysis revealed beneficial effect of UDCA on LCV growth in ADPKD compared to ADPLD. Therefore, the effect of UDCA on liver disease in ADPKD need further exploration.

Our main findings of the effect of UDCA on TLV in PLD are in line with results from an uncontrolled pilot study that reported on a 1-year UDCA treatment of 7 PLD patients [29]. The results of this study showed no statistically significant difference between liver growth one year before treatment and one year after treatment, but indicated a tendency of liver growth inhibition in the UDCA group. However, results need to be interpreted with caution as the sample size was small, no control group was included, and a very low dose of UDCA (300 mg/day) was applied [29].

A total of 15 (94%) participants in the UDCA group and 12 (71%) in the control group had at least one adverse event ($p = 0.085$) (Supplementary Table 3). Most common adverse events in the UDCA group compared to the control group were frequent stools or diarrhea (38% vs. 12%, $p = 0.017$) probably related to the study drug.

Fig. 4. Individual TLV changes in the control and UDCA group after 24 weeks. A total of 28 patients show an increase in TLV, while TLV decreases in 6 patients, 3 in the control and 3 in the UDCA group.

the stairs, one patient (control group) suffered from severe abdominal pain suspected for a liver or kidney cyst rupture, and one patient (control group) because of a shoulder injury. In addition, one patient (control group) was diagnosed with breast cancer during the trial. There were no serious adverse events related to the study drug.
Research Article

The main question that needs to be discussed is why UDCA failed to reduce TLV in our study population. Our hypothesis that UDCA reduces TLV in advanced PLD was based on experiments in PCK rats, an animal model of PLD [11,17], and on former studies on signaling properties of UDCA conjugates in hepatocytes and cholangiocytes [30]. It might be that PCK rats do not recapitulate the whole spectrum of molecular events leading to PLD in humans and that, at best, experimental observations from PCK rats can only be translated to the molecular pathophysiology of some PLD subgroups. Thus, it remains unclear whether the PLD patient population selected for this trial was the adequate target population for UDCA treatment in PLD.

Secondly, it can be debated whether PLD stage in our study population can be compared to that of the PLD stage studied in PCK rats. PCK rats received UDCA for 5 months starting at an age of 8 weeks, when the disease is mild and in progression [17,31]. In contrast, UDCA therapy was here initiated in patients with advanced PLD and who were diagnosed with PLD for a mean of 11 ± 6 years. In addition, PCK rats have a life span of 1.5 years and received UDCA for 5 months while our study population received UDCA for 6 months on a much longer life span. One could speculate that earlier and more sustained intervention with UDCA might be more effective than a short-term intervention at an advanced stage of PLD [17].

A third explanation might be that the effect of UDCA is smaller than the effect size we powered on. The a priori calculated number of patients needed for our study was based on the power to detect a clinical difference of at least 4% of TLV over 6 months, but not LCV as tested in PCK rats. This effect size was based on former studies with somatostatin analogues [28]. It is possible that UDCA affects liver volume in PLD, but the short-term effect would be smaller than that seen with a 6 month-course of somatostatin analogues [6–8]. In addition, it remains unclear whether longer UDCA treatment (2–4 years) in ADPKD could be more effective than long-term somatostatin treatment considering that LCV was reduced in ADPKD after 6 months in our study.

Interestingly, our results showed a significant improvement in HRQL after UDCA treatment, as measured by EORTC questionnaire, while scores on other HRQL and symptom questionnaires remained unchanged. As change in TLV after 24 weeks of UDCA treatment did not differ compared to change of TLV in the control group, chance or a placebo effect might be the root cause for the improvement in HRQL.

This brings us to the first limitation of our trial: the lack of double-blinding for treatment allocation. However, the primary outcome change in TLV, was analysed in a blinded objective fashion. Therefore, we assume that the absence of blind patients and physicians did not affect our primary outcome. Despite this, it could affect secondary outcomes such as HRQL and symptom burden. Secondly, our study was not powered for subgroup analyses of ADPKD and ADPLD patients. Thus, subgroup analyses were explorative by nature. The positive effects of UDCA treatment on LCV in the subgroup of patients with ADPKD, although borderline significant, are intriguing and might be studied in the future.

The international multicenter design of our trial was our key strength as it increases the generalizability of our findings. Another absolute strength of our trial is that we included a control group and were able to compare the effect of UDCA to standard of care.

In conclusion, UDCA administration showed no benefit in reducing TLV in advanced symptomatic PLD patients but decreased LCV growth in ADPKD patients. Further exploration of differences between ADPKD and ADPLD patients in the treatment response to UDCA, minimum duration and dose of UDCA treatment, appear warranted. Future studies should also focus on unraveling additional molecular targets involved in cystogenesis of different forms of PLD.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. The CURSOR trial is an investigator-initiated clinical trial.

Authors’ contributions

HD participated in the design of the trial and carried out the trial. HD had access to all of the data and performed statistical analyses. HD and MN performed analyses of liver volumes. EB performed analyses of liver cyst volumes. HD, IR, JB, RT, UB, and WK drafted the manuscript and participated in the design of the study. IR, LB and JB carried out the trial in Spain, RT and UB carried out the trial in Amsterdam. JD, conceived the study, and participated in its design. JB, UB, JD and WK helped to draft the manuscript. All authors read and approved the final manuscript.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2016.05.009.

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