Research Article

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

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Background & Aims: Ursodeoxycholic acid (UDCA) inhibits proliferation of polycystic human cholangiocytes *in vitro* and hepatic cystogenesis in a rat model of polycystic liver disease (PLD) *in vivo*. Our aim was to test whether UDCA may beneficially affect liver volume in patients with advanced PLD.

Methods: We conducted an international, multicenter, randomized controlled trial in symptomatic PLD patients from three tertiary referral centers. Patients with PLD and total liver volume (TLV) $\geqslant$2500 ml were randomly assigned to UDCA treatment (15–20 mg/kg/day) for 24 weeks, or to no treatment. Primary endpoint was proportional change in TLV. Secondary endpoints were change in symptoms and health-related quality of life. We performed a post-hoc analysis of the effect of UDCA on liver cyst volume (LCV).

Results: We included 34 patients and were able to assess primary endpoint in 32 patients, 16 with autosomal dominant polycystic kidney disease (ADPKD) and 16 with autosomal dominant polycystic liver disease (ADPLD). Proportional TLV increased by 4.6 ± 7.7% (mean TLV increased from 6697 ml to 6954 ml) after 24 weeks of UDCA treatment compared to 3.1 ± 3.8% (mean TLV increased from 5512 ml to 5724 ml) in the control group ($p = 0.493$). LCV was not different after 24 weeks between controls and UDCA treated patients ($p = 0.848$). However, UDCA inhibited LCV growth in ADPKD patients compared to ADPKD controls ($p = 0.049$).

Conclusions: UDCA administration for 24 weeks did not reduce TLV in advanced PLD, but UDCA reduced LCV growth in ADPKD patients. Future studies might explore whether ADPKD and ADPLD patients respond differently to UDCA treatment.

Lay summary: Current therapies for polycystic liver disease are invasive and have high recurrence risks. Our trial showed that the drug, ursodeoxycholic acid, was not able to reduce liver volume in patients with polycystic liver disease. However, a subgroup analysis in patients that have kidney cysts as well showed that liver cyst volume growth was reduced in patients who received ursodeoxycholic acid in comparison to patients who received no treatment.

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Keywords: Polycystic liver disease; Ursodeoxycholic acid; CT volumetry; Autosomal dominant polycystic kidney disease; Quality of life.

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Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; AP, alkaline phosphatase; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; Ca^{2+}_i, intracellular calcium; cAMP, cyclic adenosine monophosphate; CT, computed tomography; EORTC, European organization for research and treatment for cancer quality of life questionnaire; ECOG, Eastern cooperative oncology group – performance status; GGT, gamma-glutamyltransferase; HRQL, health-related quality of life; hTKV, height-adjusted total kidney volume; hTLV, height-adjusted total liver volume; LCV, liver cyst volume; MRI, magnetic resonance imaging; PKD, polycystic kidney disease; PLD, polycystic liver disease; PLD-Q, polycystic liver disease questionnaire; SF-36, medical outcomes study 36-item short-form health survey; TKV, total kidney volume; TLV, total liver volume; UDCA, ursodeoxycholic acid; VAS-EQ5D, visual-analogue scale score of the European quality of life-5 dimension.

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 *PRKCSH*, *SEC63* or *LRP5* [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_i^{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 human PLD, have increased intracellular cAMP levels and diminished Ca_i^{2+} levels compared to normal human cholangiocytes. Experimental restoration of the Ca_i^{2+} levels with a calcium ionophore inhibited cAMP-mediated hyperproliferation of PCK rat cholangiocytes [11]. Thus, strategies aimed to normalize the reduced Ca_i^{2+} levels in polycystic cholangiocytes are considered of potential therapeutic value [10].

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_i^{2+} levels in polycystic human cholangiocytes in culture and decreases hepatic cystogenesis in PCK 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 (MRI) 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 (Ursochol, 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 Pinnacle3® version 9.6 g (Philips 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 TLV segmentation exported from Pinnacle (border voxelized at midpoint, in order to reproduce pinnacle TLV values), and Otsu thresholding (512 bins) was

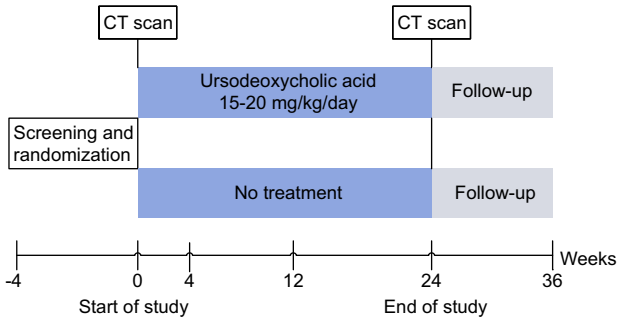

Fig. 1. Trial design of the CURSOR trial. Patients were screened for eligibility and eligible patients were randomized in an equal ratio to either the UDCA group or the control group. All patients received a CT scan at baseline and 24 weeks. Control visits were performed at week 4, 12 and 24 after baseline. A follow-up visit was performed 12 weeks after end of study (week 36).