New Advances in Polycystic Liver Diseases

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Polycystic liver diseases (PLDs) are congenital genetic cholangiopathies characterized by bile duct dilation and/or the development of multiple (>20) fluid-filled biliary cysts, which are the main cause of morbidity in these patients.1,2 According to the particular mutation involved, these diseases may be found alone or in association with polycystic kidney disease (PKD). The PLD phenotype is heterogeneous with high intrafamilial variability. Both men and women can develop PLD; however, females usually show a more aggressive phenotype probably linked to hormonal differences (presumably higher estrogen levels).1,2 In some patients, PLD may remain asymptomatic, whereas in others the disease is characterized by the development of hepatomegaly together with multiple symptoms and complications, such as abdominal distention and bloating, back pain, gastroesophageal reflux, dyspnea, and hypertension, as well as infection, hemorrhage, cyst rupture, and more.1

To date, the only curative option for symptomatic PLDs is liver transplantation. Different surgical procedures such as aspiration-sclerotherapy, fenestration, segmental hepatic resection, and selective embolization of the hepatic arterial branches are commonly employed to eliminate symptomatic cysts; however, these approaches have inherent risks and are not able to block disease progression.1 To find novel molecular

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targets for the pharmacological treatment of PLDs, an increasingly number of studies have been performed to investigate the molecular mechanisms involved in the pathogenesis of these diseases. As a result, it is now known that hepatic cystogenesis may arise from ductal plate malformation (DPM) during embryogenesis, loss of heterozygosity (LOH) linked to second-hit mutations, and/or centrosome and primary cilium abnormalities in cholangiocytes. Over PC-2 can also be found in the ER membrane where it works as a coreceptor transducing promitotic signals linked to Wnt signaling.

Here we will outline the current insights on PLDs, focusing on the most novel and significant discoveries at the molecular and therapeutic levels.

**Etiology**

**Genetics**

Polycystic liver diseases are caused by different germline mutations responsible for the development of isolated hepatic cysts (i.e., autosomal dominant polycystic liver disease [ADPLD]: ~1:100,000) or hepatorenal cystogenesis (i.e., autosomal dominant polycystic kidney disease [ADPKD]: ~1:600–1,000) or autosomal recessive polycystic kidney disease [ARPKD], Caroli’s disease, or congenital hepatic fibrosis [CHF] in infants: ~1:20,000).

Autosomal dominant polycystic liver disease is triggered by mutations in PRKCSH, SEC63, or LRPS genes (→ Fig. 1), with PRKCSH being the most common one (~15%). PRKCSH and SEC63 encode for hepatocystin and SEC63, respectively, both endoplasmic reticulum (ER) resident proteins. Hepatocystin corresponds to the noncatalytic β-subunit of glucosidase II (GIIβ) that is involved in the appropriate conformation and folding of glycoproteins, whereas SEC63 mediates the protein translocation throughout the ER membrane. Furthermore, LRPS encodes for the transmembrane protein LRPS that works as a coreceptor transducing promitotic signals linked to Wnt signaling. However, these three mutated genes only explain ~20% of all ADPLD cases, whereas the mutation is unknown in the remaining ~80%. On the other hand, mutations in PKD1 (~80–85%) and PKD2 (~10–15%) genes underlie ADPKD and affect the liver in ~85% of these patients. PKD1 encodes for the mechanoreceptor polycystin-1 (PC-1) and PKD2 for the nonselective calcium channel polycystin-2 (PC-2) (→ Fig. 1). Coupled together, PC-1 and PC-2 form a mechanosensitive complex in the primary cilium of cholangiocytes that regulates intracellular Ca²⁺ homeostasis. Moreover, PC-2 can also be found in the ER membrane where it modulates [Ca²⁺]. Finally, mutations in PKHD1 are causative for ARPKD, which is characterized by the absence or aberrant function of fibrocystin (FC)/polyductin, a protein involved in tubulogenesis and the maintenance of the duct lumen epithelium architecture. Particular mutations in PKHD1 can also result in the development of other clinical forms of disease such as Caroli disease and/or CHF.

As mentioned above, there is a proportion of ADPLD (~80%) and ADPKD (~10%) patients with no mutations detected. Notably, a recent study in genetically unresolved ADPKD families has identified a new mutated gene, GANAB (11q12.3), which encodes for the catalytic α-subunit of glucosidase II (GIIα) in the ER (→ Fig. 1). Whole-exome sequencing analysis revealed different types of GANAB gene mutations (i.e., frameshift, splicing, nonsense, and missense mutations). In GANAB−/− cells, the loss of GIIα function results in aberrant maturation and ciliary localization of PC-1 and PC-2, which are associated with disease severity. The global phenotype related to GANAB mutations holds mild renal signs with highly variable liver disease, ranging from no cyst to severe clinical manifestations. Of note, defects in PC-1 expression and/or maturation are considered the main cause of cystogenesis in PLD.

Although some PLDs are considered phenotypically dominant according to the germline mutations, these might not be enough to trigger disease development and progression. Thus, spontaneous somatic second-hit mutations that inactivate the wild-type allele may occur. Accordingly, both alleles of PLD-related genes become inactivated, leading to LOH that aggravates the progression and severity of the disease. A high proportion of patients with PRKCSH germline mutation exhibits LOH, whereas only a few acquire SEC63 LOH. In addition, somatic second-hit mutations have also been disclosed in ADPKD patients showing a larger impact in PKD1 than PKD2.

**Ductal Plate Malformation**

Polycystic liver diseases prosper as a consequence of DPM during embryogenesis, which is promoted by the aberrant expression of different growth factors, transcription factors, and microRNAs (miRNAs). Several pathological mechanisms have been proposed for DPM and cyst development, including aberrant hepatoblast differentiation, defects in the primitive ductal structure maturation, and perturbation of bile duct enlargement during development. In this regard, evidence suggests that ARPKD is mainly the result of abnormal duct expansion, whereas ADPLD and ADPKD could involve multiple pathogenic mechanisms.

**Molecular Mechanisms of Pathogenesis**

**Primary Cilium Dysfunction**

The primary cilium of cholangiocytes is a sensory tubular organelle extending from the apical membrane into the bile duct lumen. It is formed by a centriole-derived basal body and an axoneme (i.e., 9 + 0 microtubule pattern) and is composed of specific receptors and channels able to detect extracellular stimuli—mechanical, chemical, and osmotic signals—and transduce them toward the intracellular machinery ultimately regulating diverse functions, such as differentiation, planar cell polarity, homeostasis, and proliferation. Mutations affecting PKD1 and PKD2 genes may...
generate nonfunctional PC-1 and PC-2 proteins resulting in abnormal cilia due to decreased size and/or aberrant structure, which subsequently decrease $[Ca^{2+}]_i$ and increase cAMP levels, thus promoting cholangiocyte hyperproliferation and impaired secretory/absorptive functions. On the other hand, mutations in PKRCSH and SEC63 trigger the aberrant biogenesis of PC-1 and PC-2 proteins within the ER, resulting in the disruption of the steady-state balance of the PC-1/PC-2 complex. PC-1 seems to be more susceptible to undergo defective maturation within the ER; therefore, it is considered the rate-limiting component in the severity and onset of cyst formation. In addition, PLDs are characterized by defects in centrosome duplication during the cell cycle that underlie morphological (i.e., size of cilium) and functional (i.e., cellular location of cilium) abnormalities of the primary cilium in cystic cholangiocytes and promote hepatic cystogenesis.

**Dysregulated Ca$^{2+}$ and cAMP Levels**

Cystic cholangiocytes are characterized by increased cAMP levels and decreased $[Ca^{2+}]_i$, leading to hyperproliferation. Aberrant expression/function of either PC-1 and/or PC-2 proteins leads to depletion of both cytoplasmic...
and ER calcium stores.\textsuperscript{37} Notably, decreased [Ca\textsuperscript{2+}], induces cAMP synthesis via adenylate cyclase 6 (AC6) activation and also inhibits phosphodiesterase 1–dependent cAMP hydrolysis.\textsuperscript{37,38} Overproduction of cAMP mediates the activation of EPAC/ERK and PKA/ERK signaling pathways that stimulate cystic cholangiocyte proliferation.\textsuperscript{34} Therefore, the restoration of calcium homeostasis and/or inhibition of cAMP production represents potential therapeutic strategies for PLD patients that are discussed below (\textsuperscript{\textbullet} Fig. 1).\textsuperscript{2,34,39,40}

Enhanced Proliferation and Angiogenesis
Mutations in PLD-related genes contribute to sustain an immature biliary phenotype that makes cystic cholangiocytes more sensitive to proliferative signals. There are several mechanisms promoting cholangiocyte proliferation; however, the major proliferative stimulus is the impaired intracellular generation of cAMP that activates the Ras/Raf/MEK/ERK1/2 signaling pathway in a PKA-dependent manner (\textsuperscript{\textbullet} Fig. 1).\textsuperscript{34,41} As a result, cholangiocytes, via HIF1\textalpha activation, also increase the production and secretion of the promitotic and angiogenic factor vascular endothelial growth factor (VEGF),\textsuperscript{32,43} which interacts with its receptors VEGFR1 and VEGFR2 overexpressed in biliary cystic epithelial cells and promote the enlargement of the cysts and their vascular supply in an autocrine/paracrine way.\textsuperscript{44} A second family of vascular growth factors is comprised of angiopoietin 1 (ANG-1) and angiopoietin 2 (ANG-2) that work in parallel with VEGF to induce cholangiocyte proliferation and cyst vascularization.\textsuperscript{44} In addition, cyst epithelium is sensitive to other molecules such as growth factors (i.e., insulin-like growth factor 1 [IGF-1]), cytokines (i.e., interleukin- [IL-] 8, IL-6) and chemoattractant factors (i.e., MCP-1, ENA-78) that are highly present in the cystic fluid of PLD patients.\textsuperscript{45–47} IGF-1 induces cystic cholangiocyte proliferation and angiogenesis through VEGF secretion mediated by the mTOR pathway,\textsuperscript{48} whereas IL-6 and IL-8 are involved in both cholangiocyte proliferation and the remodeling of extracellular matrix, promoting cyst expansion.\textsuperscript{46} Of note, the administration of the mTOR inhibitor rapamycin (also called sirolimus) to Pkd2KO mice reduces cystic progression through the repression of cholangiocyte proliferation and the disturbance of angiogenesis that ultimately induces apoptosis of cystic cholangiocytes.\textsuperscript{48} Estrogens also exhibit direct and/or indirect proliferative effects by stimulating the release of IGF-1 from cystic epithelium.\textsuperscript{49}

Enhanced Peribiliary Inflammation and Fibrosis
Fibrocystin-defective diseases (i.e., ARPKD, CHF, and Caroli’s disease) are characterized by peribiliary inflammation and fibrosis, two mechanisms involved in the progression of the disease.\textsuperscript{40} In this regard, \textit{Pkhd1}^del4/del4 mice are characterized by progressive peribiliary inflammatory infiltration and subsequent portal fibrosis. In \textit{Pkhd1}^del4/del4 mouse cholangiocytes, increased cAMP stimulates the noncanonical \textbeta-catenin pathway by PKA-mediated Ser\textsuperscript{675} phosphorylation of \textbeta-catenin, which promotes its nuclear translocation and transcriptional activity, leading to enhanced cell motility.\textsuperscript{51} On the other hand, these \textit{Fc}–defective mouse cholangiocytes secrete a range of chemokines, such as CXCL1, CXCL10, and CXCL12, which recruit bone-marrow–derived macrophages through a \textbeta-catenin–dependent mechanism.\textsuperscript{50} During early phases, proinflammatory M1 macrophages are recruited to the site of damage, which predominantly release tumor necrosis factor-\textalpha. As the disease progresses, macrophages switch to an anti-inflammatory and profibrotic M2 phenotype, by secreting transforming growth factor-\textbeta1 (TGF-\textbeta1). Moreover, as a response to proinflammatory cytokines released by macrophages, \textalpha\textbeta6 integrin becomes upregulated in \textit{Pkhd1}^del4/del4 mouse cholangiocytes, thereby activating latent TGF-\beta1 and inducing the peribiliary deposition of collagen.\textsuperscript{50}

Altered Extracellular Matrix Remodeling
Cystic cholangiocytes are characterized by increased MMP activity that promotes the digestion and remodeling of extracellular matrix.\textsuperscript{4–47} These cells secrete increased levels of IL-6 and IL-8 that promote, in an autocrine/paracrine way, the expression of different MMPs resulting in cell MMP hyperactivity. Estrogens also stimulate the MMP activity of cystic cholangiocytes.\textsuperscript{47}

Altered Secretion
One major physiological function of cholangiocytes is the fluidization and alkalinization of hepatocytes-derived bile and the regulation of its composition through secretory and reabsorptive processes.\textsuperscript{52,53} Enhanced fluid secretion into the cystic lumen plays a key role in hepatic cystogenesis, being modulated by different hormones, receptors, and transporters.\textsuperscript{2,54} Secretin is a gastrointestinal hormone that promotes cAMP synthesis in cholangiocytes through binding to the secretin G-protein coupled receptor localized in the basolateral membrane, which is coupled to adenylyl cyclases.\textsuperscript{53,55} The resultant intracellular cAMP increase facilitates fluid secretion by exocytosis of vesicles containing the chloride channel cystic fibrosis transmembrane conductance regulator (CFTR), the Cl\textsuperscript{−}/HCO\textsuperscript{−}\textsubscript{3} exchanger AE2 (anion exchange protein 2), and the water channel aquaporin 1 (AQPI) into the apical membrane of cholangiocytes.\textsuperscript{52,54,56} Activation of CFTR promotes the apical release of chloride that is exchanged with bicarbonate via AE2 and is the driving force for the movement of water through AQPI.\textsuperscript{53} Overexpression and mislocalization of these plasma membrane proteins are associated with altered fluid secretion in PLDs.\textsuperscript{54} Notably, intravenous administration of secretin to ADPKD patients resulted in enhanced fluid secretion through the hepatic cystic epithelium.\textsuperscript{57} On the other hand, bile acids (BAs) secreted by hepatocytes are key players in the regulation of canalicular bile flow (i.e., bile-acid-dependent bile flow).\textsuperscript{53} In addition, BAs are signaling molecules able to regulate different functions in cholangiocytes such as proliferation.\textsuperscript{40} Impaired BA homeostasis is associated with the pathogenesis of PLDs. A recent study showed that PCK rats (an animal model of ARPKD) present increased intrahepatic levels of BAs, particularly of the most cytotoxic BA species, which results in decreased BA concentration in the bile that exits the liver.\textsuperscript{40} Of note, this high intrahepatic concentration of BAs is not associated with changes in the expression of \textit{Cyp7a1},\textsuperscript{40} the rate-limiting enzyme of BA synthesis in the liver. The cystic fluid of PLD patients is also more concentrated in BAs when compared with their matched serum levels; some of these BAs stimulate the proliferation of cystic cholangiocytes, thus promoting hepatic cystogenesis.\textsuperscript{40}
Epigenetics
Polycystic liver diseases are characterized by epigenetic modifications that promote cell proliferation. Global changes in the miRNA expression profile are present in cystic cholangiocytes. In PCK cholangiocytes, most of the dysregulated miRNAs are found downregulated (~89%), which is associated with overexpression of multiple proteins involved in proliferation and secretion. In particular, miRNA-15a is highly downregulated in both rat and human cystic cholangiocytes, promoting the overexpression of the cell division cycle 25 homolog A (Cdc25A) protein that induces cell proliferation and cyst growth. In addition, miR-30a, important for ductal plate formation, is downregulated in human cystic cholangiocytes.

Histone deacetylase 6 (HDAC6) is a member of the HDAC family that epigenetically regulates gene expression. However, in contrast to the other HDACs, HDAC6, is predominantly localized in the cytoplasm of cells and is not involved in the epigenetic regulation of gene expression. HDAC6 is involved in the regulation of multiple cellular processes including cell cycle. Overexpression of HDAC6 occurs in cystic cholangiocytes and promotes the deacetylation of α-tubulin present in the primary cilium, which may result in ciliary malformation and dysfunction. Moreover, HDAC6 regulates Wnt-signaling by deacetylating β-catenin, promoting cell proliferation.

Pharmacological Therapies with Beneficial Outcomes
The study of the molecular mechanisms involved in the pathogenesis of PLDs has resulted in the evaluation of different pharmacological strategies in preclinical studies and clinical trials. Some of these preclinical studies have shown positive therapeutic value, such as the use of MMP inhibitors, Cdc25A inhibitors (i.e., vitamin K3, PM-20), HDAC6 inhibitors, PPAR-γ agonists, VEGFR2 inhibitors, or Trpv4 activators, but their clinical evaluation has not been performed yet. On the other hand, other therapeutic strategies with positive preclinical value did not meet the clinical expectations such as the use of mTOR inhibitors. Thus, the pharmacological strategies with positive clinical outcomes are mainly based on the normalization of the intracellular cAMP and calcium levels in cystic cholangiocytes.

Somatostatin Analogs
Somatostatin analogs represent a potential therapeutic strategy owing to its ability to suppress cAMP production. Several studies have reported the beneficial effects attributed to the administration of somatostatin analogs in both PLDs animal models and patients. Preclinical studies performed in PCK rats treated with octreotide have disclosed a significant reduction in cAMP levels, hepatic cystic volume and fibrosis, and liver weight and proliferation rate in a time- and dose-dependent manner. Additionally, these beneficial effects have been boosted by the administration of pasireotide, a more potent somatostatin analog with a broader range of somatostatin receptors binding to different PLD animal models. Notably, renal cystogenesis was also reduced when somatostatin analogs were administrated. To date, several clinical trials have been performed to evaluate the safety, efficacy, and therapeutic value of the somatostatin analogs octreotide and lanreotide (Table 1), whereas the efficacy of pasireotide is currently being assessed clinically. Octreotide (40 mg) and lanreotide (120 mg) exhibit their major effects during the first 6 months of treatment resulting in significant reduction of total liver volume (TLV; -5%) in ADPLD and ADPKD patients; these drugs also ameliorate the health-related quality of life, but produce several side effects (i.e., gallbladder stones, diarrhea, nausea, vomiting, dizziness, and headache). A pooled analysis of three different clinical studies showed that young female patients (≤48 years old) have the greatest benefit of somatostatin analog therapy, whereas the effect in males was not apparent. On the other hand, prolonged therapy with somatostatin analogs, such as 12 months for lanreotide or up to 4 years for octreotide, did not result in better outcomes than treatment for 6 months, but seems to maintain the beneficial effects and prevent the rebound effects on liver volume. In contrast, somatostatin analogs decrease total kidney volume (TKV) in ADPKD patients after 6 to 12 months of treatment, but this effect is not further extended when treatments are prolonged to 2 to 4 years. Of note, chronic treatment (18 months) of PLD patients with somatostatin analogs induces relevant side effects such as loss of body weight and sarcopenia.

Ursodeoxycholic Acid
Ursodeoxycholic acid (UDCA; 3a,7b-dihydroxy-5b-cholanoic acid) is an endogenous hydrophilic bile acid with hepatoprotective properties on both cholangiocytes and hepatocytes. Oral supplementation of UDCA promotes a bicarbonate-rich choleresis in humans resulting in reduced hepatic concentration of the most cytotoxic BA species. Ursodeoxycholic acid administration is also able to inhibit biliary hyperplasia characteristic of experimental models of biliary obstructive cholestasis such as bile duct ligation. Notably, these beneficial effects are partially mediated by restoration of the [Ca2+]i in cholangiocytes. In this regard, UDCA is the only drug approved by the U.S. Food and Drug Administration for the treatment of patients with primary biliary cholangitis, showing important beneficial effects in approximately two-thirds of patients.

In PLDs, the effect of UDCA was evaluated in both preclinical models and a clinical trial. Chronic administration of UDCA to young PCK rats blocked hepatic cystogenesis and fibrosis and improved their physical fitness. In this regard, UDCA inhibited baseline cystic cholangiocyte hyperproliferation and also the proliferation stimulated by promitotic bile acids. On the other hand, UDCA treatment decreased the hepatic concentration of the most cytotoxic BAs and normalized the BA concentration in the bile of PCK rats. These beneficial effects were associated with the normalization of the intracellular Ca2+ in cystic cholangiocytes (Fig. 1). As a consequence of these positive data, an international multicenter phase II clinical trial was performed to evaluate the potential therapeutic value of UDCA.
Table 1 Clinical trials with positive outcomes for polycystic liver diseases

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Design</th>
<th>Patients</th>
<th>Drug administration</th>
<th>Main outcomes</th>
<th>Adverse events</th>
<th>References</th>
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<td></td>
<td></td>
<td>Dose</td>
<td>Period</td>
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<td><strong>Somatostatin analogs</strong></td>
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<tr>
<td>NCT00426153</td>
<td>Single center randomized double-blind study</td>
<td>ADPKD (OCT, n = 24; PBO, n = 10)</td>
<td>40 mg, IM</td>
<td>12 mo (Every 28 d)</td>
<td>TLV: -4.95% (vs. +0.92% in PBO group) TKV: +0.25% (vs. +8.61% in PBO group) HRQoL (SF-36): 74.1 (vs. 59.8 baseline levels)</td>
<td>Diarrhea, abdominal cramps, nausea, gas, vomiting, dizziness, headache, injection site pain, bloating</td>
</tr>
<tr>
<td>NCT00565097</td>
<td>International multicenter randomized double-blind study</td>
<td>ADPKD (LAN, n = 12; PBO, n = 20)</td>
<td>120 mg, SC</td>
<td>6 mo (Every 28 d)</td>
<td>TLV: -2.9% (vs. -1.6% in PBO group) TKV: -1.5% (vs. -3.4% in PBO group) HRQoL (SF-36): 65 (vs. 54 in PBO group) Serum ALP: +0.1 (vs. 0.0 in PBO group) Serum γGT: +0.7 (vs. 0.7 in PBO group)</td>
<td>Diarrhea, pale stools, abdominal cramps, flatulence, constipation</td>
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<tr>
<td>NCT00771888</td>
<td>Multicenter open-label extension study</td>
<td>ADPKD (LAN, n = 25)</td>
<td>120 mg, SC</td>
<td>12 mo (Every 28 d)</td>
<td>TLV: -4% (vs. baseline levels) TKV: -1% (vs. baseline levels) HRQoL (SF-36): 56 (vs. 47 baseline levels) Serum ALP: +8.33% (vs. baseline levels) Serum γGT: -5% (vs. baseline levels)</td>
<td>Steatorrhea, abdominal cramps</td>
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Table 1 (Continued)

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<thead>
<tr>
<th>Identifier†</th>
<th>Design</th>
<th>Patients</th>
<th>Drug administration</th>
<th>Main outcomes</th>
<th>Adverse events</th>
<th>References</th>
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<tbody>
<tr>
<td>NCT01315795</td>
<td>Multicenter open-label extension study</td>
<td>ADPKD (n = 35); ADPLD (n = 8)</td>
<td>90 mg, SC; 120 mg, SC</td>
<td>TLV: -2.34% (vs. baseline levels)</td>
<td>Steatorrhea, abdominal cramps, sarcopenia, weight loss</td>
<td>Temmerman et al. (2015)76</td>
</tr>
<tr>
<td>NCT00565097</td>
<td>Individual patient data pooled analysis</td>
<td>PLDs (90 mg LAN, n = 55); PLDs (120 mg LAN, n = 51); PBO (n = 26)</td>
<td>90 mg LAN; 120 mg LAN, SC</td>
<td>Varying from 6–12 mo</td>
<td>TLV: (90 mg) -1.4%, (120 mg) -2.8% (vs. +1.1% in PBO group) TKV: (90 mg) -1.15%, (120 mg) -16.2% (vs. +25% in PBO group)</td>
<td>Diarrhea, steatorrhea, pale stool, abdominal cramps, flatulence, constipation</td>
</tr>
<tr>
<td>NCT00426153</td>
<td>Individual patient data pooled analysis</td>
<td>PLDs (n = 17); PBO (n = 52)</td>
<td>120 mg LAN, sc; 40 mg OCT, IM</td>
<td>Varying from 6–12 mo</td>
<td>TLV: Low (&lt;4,256 mL): -4.5% (vs. PBO group) High (&gt;4,256 mL): -6.5% (vs. PBO group) Women, &lt;48 y: -8.0% (SA vs. PBO group); Women, &gt;48 y: -4.1% (SA vs. PBO group)</td>
<td>Diarrhea/loose stools, abdominal cramps, flatulence, bloating, gas, steatorrhea, persistent injection-site swelling</td>
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<tr>
<td>NCT02021110</td>
<td>International Multicenter Randomized</td>
<td>ADPKD (UDCA, n = 9; PBO, n = 7); ADPLD (UDCA n = 6; PBO, n = 10)</td>
<td>15–20 mg/kg, oral</td>
<td>6 mo (Every day)</td>
<td>TLV: +4.6% (vs. +3.1% in PBO group); TKV: +0.6% (vs. +0.5% in PBO group); LCV increase (ADPKD): +81 mL (vs. +470 mL in PBO group)* HRQoL (EORTC): 26 (vs. 32 in PBO group)6 Serum ALP: -0.15 (vs. -0.04 in PBO group) Serum ALP: 0.83 (vs. 1.04 baseline levels) Serum γGT: -1.13 (vs. -0.07 in PBO group)</td>
<td>Frequent stools/diarrhea</td>
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Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ALP, alkaline phosphatase; EORTC, European organization for research and treatment of cancer quality of life questionnaire; γGT, gamma-glutamyl transpeptidase; HRQoL, health-related quality of life; IM, intramuscular; LAN, Lanreotide; LCV, liver cyst volume; NCT, national clinical trial; OCT, Octreotide; PBO, placebo; PLDs, polycystic liver diseases; RCTs, randomized clinical trials; SA, somatostatin analogs; SC, subcutaneous; SF-36, MOS 36-item short form health survey; TKV, total kidney volume; TLV, total liver volume; UDCA, ursodeoxycholic acid.

Note. Data on “main outcomes” are mean values.

†https://clinicaltrials.gov.

*Placebo group crossed over to treatment and vice versa.

‡Participants were off OCT therapy for a mean of 8.3 months after completion of the original 2-year clinical trial.

§Scores in subdomain physical body functioning.

∥Placebo group crossed over to treatment for 12 months and lanreotide group continued treatment for additional 6 months.

*p < 0.05.
supplementation to highly symptomatic PLD patients (i.e., ADPKD and ADPLD) with advanced disease (> 20 cysts and TLV > 2,500 mL) (<Table 1>). UDCA administration was well tolerated and no major side effects were observed rather than frequent stools and diarrhea (38% vs. 12% of patients with UDCA or nontreatment, respectively). Oral administration of UDCA for 6 months (i.e., 15–20 mg/kg/d) did not show significant differences on TLV between UDCA-treated and nontreated groups. However, subgroup analysis revealed a significant increase in both TLV (4.6%) and TKV (20 mL) in nontreated ADPKD patients, whereas no differences on both parameters were observed in ADPKD patients treated with UDCA (TLV increase = 2.6% and TKV increase = 10 mL). Regarding liver cystic volume (LCV), UDCA administration significantly inhibited the LCV increase in ADPKD patients compared with nontreated ADPKD patients. In contrast, this beneficial effect was not reflected in ADPLD patients. On the other hand, the levels of the serological biomarkers γ-glutamyl transpeptidase (γGT) and alkaline phosphatase underwent a significant reduction in the UDCA group, but not in the nontreated group. Notably, γGT levels in the UDCA group were significantly lower than in the control group.

In line with this, a pilot study in Japan on a small cohort of PLD patients had also reported beneficial effects of UDCA in the regulation of alkaline phosphatase and γGT elevated levels. Both biliary enzymes were significantly reduced after 1 year of UDCA treatment (300 mg/d). Additionally, UDCA had an inhibitory tendency on TLV growth in these PLDs patients, albeit with no significant changes.

**Conclusion**

In the last few years, significant advances in the determination of the genetic bases and pathological mechanisms involved in the pathogenesis of PLDs have been made. This valuable information has allowed the improved classification of patients according to genotype and phenotype, and has provided a better understanding of the molecular mechanisms involved in the pathogenesis of PLD, resulting in new therapeutic strategies. To date, the chronic administration of somatostatin analogs represents a beneficial approach in the treatment of PLDs, particularly in middle-aged women, due to its capacity to reduce the TLV and to improve quality of life. Nevertheless, the absence of additional beneficial effects in long-term treatment with somatostatin analogues, the high economic burden, and the frequent side effects of this treatment make it necessary to develop alternative therapeutic strategies. In this regard, the choleretic and hepatoprotective properties of UDCA have led this endogenous BA to emerge as a promising pharmacological option because it represses the progressive LCV increase in ADPKD, although not in ADPLD, and improves the symptoms of treated patients.

**Abbreviations**

<table>
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<tr>
<th>Acronym</th>
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<tr>
<td>γGT</td>
<td>γ-glutamyl transpeptidase</td>
</tr>
<tr>
<td>AC6</td>
<td>adenylate cyclase 6</td>
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<tr>
<td>ADPKD</td>
<td>autosomal dominant polycystic kidney disease</td>
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<tr>
<td>ADPLD</td>
<td>autosomal dominant polycystic liver disease</td>
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<tr>
<td>AE2</td>
<td>anion exchange protein 2</td>
</tr>
<tr>
<td>ANG</td>
<td>angiopoietin</td>
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<tr>
<td>AQP1</td>
<td>aquaporin 1</td>
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<tr>
<td>ARPKD</td>
<td>autosomal recessive polycystic kidney disease</td>
</tr>
<tr>
<td>BA</td>
<td>bile acids</td>
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<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<tr>
<td>Cdc25A</td>
<td>cell division cycle 25 homolog A</td>
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<tr>
<td>CFTR</td>
<td>cystic fibrosis transmembrane conductance regulator</td>
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<td>CHF</td>
<td>congenital hepatic fibrosis</td>
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<tr>
<td>DPM</td>
<td>ductal plate malformation</td>
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<td>ER</td>
<td>endoplasmic reticulum</td>
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<tr>
<td>FC</td>
<td>fibrocystin</td>
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<tr>
<td>GIIα</td>
<td>α-subunit of glucosidase II</td>
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<tr>
<td>GIIβ</td>
<td>β-subunit of glucosidase II</td>
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<td>HDAC6</td>
<td>histone deacetylase 6</td>
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<td>hypoxia-inducible factor 1-alpha</td>
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<tr>
<td>IGF-1</td>
<td>insulin-like growth factor 1</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
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<tr>
<td>LCV</td>
<td>liver cystic volume</td>
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<tr>
<td>LOH</td>
<td>loss of heterozygosity</td>
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<td>LRPS</td>
<td>low density lipoprotein receptor-related protein 5</td>
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<tr>
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<td>microRNA</td>
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<td>matrix metalloproteinase</td>
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<td>PC</td>
<td>polycystin</td>
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<tr>
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<td>polycystic liver disease</td>
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<tr>
<td>PRKCSH</td>
<td>protein kinase C substrate 80K-H</td>
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<tr>
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<td>SEC63 homolog</td>
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<td>TGF-β1</td>
<td>transforming growth factor-β1</td>
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<tr>
<td>TKV</td>
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<tr>
<td>Trpv4</td>
<td>transient receptor potential cation channel subfamily V member</td>
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<tr>
<td>TLV</td>
<td>total liver volume</td>
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<tr>
<td>UDCA</td>
<td>urodeoxycholic acid</td>
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<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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**Future Directions**

There are still PLD patients with undetermined gene mutations deserving future investigation. Further studies on the molecular mechanisms involved in the pathogenesis of every type of PLD are needed to provide new therapeutic approaches. In this particular context, effective therapeutic strategies are still absent for ARPKD-related liver disease, representing a major clinical problem. In addition, future international multicenter clinical trials with larger cohorts of PLD patients (i.e., ADPKD and ADPLD) are desirable to analyze in detail the effects of the long-term administration of somatostatin analogs. Moreover, long-term UDCA therapy should be assessed in early and advanced stages of the disease, as well as the potential differences in response between ADPKD and ADPLD patients. Finally, a dual therapy combining somatostatin analogs and UDCA should be evaluated in the near future.
because this promising pharmacological alternative may exert additive/synergetic effects resulting in more effective management of symptoms and disease progression.

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