Medical and Surgical Treatment Options for Polycystic Liver Disease

Joost P.H. Drenth,[1] Melissa Chrispijn,[1] David M. Nagorney,[2] Patrick S. Kamath,[3] and Vicente E. Torres[4]

Brief Introduction to the Polycystic Liver Disorders

A hepatic cyst is a fluid-filled, epithelial lined cavity which varies in size from a few milliliters to several liters. Unlike single cysts, polycystic liver, which is arbitrarily defined when >20 cysts are present, is a rare condition and is part of the phenotype of two inherited disorders. In autosomal dominant polycystic kidney disease (ADPKD), patients have polycystic kidneys and may eventually develop polycystic liver disease (PLD).[1] In autosomal dominant polycystic liver disease (PCLD), multiple hepatic cysts are the primary presentation, whereas polycystic kidneys are absent.[2] Traditionally, treatment consists of physical removal or emptying of cysts by a range of invasive techniques.[3] However, there has been considerable progress in the development of new medical modalities over the last few years. Therefore, it is timely to review recent advances focused on promising novel therapies for this disease.

Clinical Presentation and Epidemiology

ADPKD is the most prevalent inherited renal disorder, with a prevalence of 0.1%-0.2%.[1,3] The prevalence of PCLD is not known, but it is likely underrecognized.[2] Although PCLD and ADPKD are distinct at the genetic level, both disorders have polycystic livers in common. The clinical presentation of ADPKD is well known, but the clinical profile of PCLD is poorly defined, and much of the information available so far stems from extrapolation of studies in ADPKD. The common thinking is that the natural history of PLD is compatible with a continuous growth in number and size of cysts. Data from three recent trials[4–6] indicate that the annual growth of polycystic livers is ~0.9%-3.2% (Fig. 5). The prevalence of hepatic cysts in ADPKD is high (67%-83%), and is likely age-dependent.[7,8] Risk factors for cyst growth are age, female sex, and renal cyst volume.[8] In addition, severity of renal cystic disease, prior pregnancies, and estrogen use predict increase of polycystic liver size in ADPKD.[7,9] Indeed, 1 year of estrogen use in postmenopausal ADPKD patients selectively increases total liver volume by 7%, whereas total kidney volume remains unaffected.[2,10]

Symptoms in PLD are probably secondary to the increased total liver volume.[10] As polycystic livers can grow up to 10 times their normal size, they compress adjacent abdominal and thoracic organs. Patients with massively enlarged polycystic livers suffer from epigastric pain, abdominal distension, early satiety, nausea, or vomiting. Typically, dress size increases, and patients are unable to see their feet, cut toenails, and bend over. Patients with grossly enlarged livers develop abdominal wall herniation and may report shortness of breath. Other complications are infection, hemorrhage or rupture of a cyst, compression of the inferior cava, hepatic veins, or bile ducts, but these occur less frequently.[2]

Pathogenesis of Cyst Formation

Both ADPKD and PCLD are autosomal dominant disorders. Two gene mutations account for almost all ADPKD cases: *PKD1*, which encodes polycystin-1, accounts for 85% of cases, whereas *PKD2*, encoding polycystin-2, is responsible for the remainder. PCLD is caused by *PRKCSH* or *SEC63* mutations, although in

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; cAMP, 3′-5′-cyclic adenosine monophosphate; mTOR, mammalian target of rapamycin; PCLD, polycystic liver disease; TAE, transcatheter arterial embolization; VEGF, vascular endothelial growth factor.

From the [1]Department Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, The Netherlands; [2]Division of Gastroenterologic and General Surgery, Mayo Clinic College of Medicine, Rochester, MN; [3]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN; [4]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, MN.

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Address reprint requests to: Joost P.H. Drenth, Department Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, The Netherlands. E-mail: joostphdrenth@cs.com; fax: +31 24 3540103.

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only 21% of patients a bonafide mutation can be found.[11,12] The protein products of these genes (hepatocystin and Sec63, respectively) act in concert to achieve proper topology and folding of integral membrane or secreted glycoproteins in the endoplasmic reticulum (ER).[13]

Liver cysts are thought to arise from malformation of the ductal plate during embryonic liver development. Normal bile ducts arise from the ductal plate through growth and apoptosis. In PLD, complexes of disconnected intralobular bile ductules, also termed von Meyenburg complexes, are retained. These complexes can grow into cysts in adult life and become disconnected as they grow from von Meyenburg complexes.[14-16]

Probably, abnormalities in biliary cell proliferation and apoptosis and enhanced fluid secretion are key elements in the pathogenesis of PLD. In cystic livers, activation of several signal transduction pathways is altered leading to hyperproliferation and hypersecretion. Indeed, vascular endothelial growth factor (VEGF), estrogens, and insulin-like growth factor-1 are overexpressed in hepatic cystic epithelium, and promote cholangiocyte proliferation in an autocrine fashion.[17,18] Additionally, markedly higher levels of phospho-ERK, phospho-AKT, phospho-mammalian target of rapamycin (mTOR), and its downstream effector phospho-S6 ribosomal protein (S6rp) are found in hepatic cysts.[19] Finally, the second messenger 3′-5′-cyclic adenosine monophosphate (cAMP) regulates cholangiocyte proliferation and fluid secretion.[20] There are higher cAMP levels in cholangiocytes of ADPKD rodent models, which is associated with cholangiocyte hyperproliferation and cyst expansion.[21,22]

Laboratory Findings

There are no specific laboratory test abnormalities of PLD. As a rule, liver synthesis is maintained during all stages of the disease. Gamma glutamyl transferase (gGT) is elevated in 51% and a high alkaline phosphatase (AP) is seen in 17% of PCLD patients.[2] The elevated AP and gGT levels probably reflect activation of cholangiocytes.[9,23-26] Serum transaminases are normal or only mildly elevated.[2] Bilirubin is rarely elevated but in advanced cases jaundice may arise due to compression of the common bile duct secondary to a strategically located cyst.

CA19-9, a biomarker that is clinically used to differentiate benign from malignant gastrointestinal disorders, is elevated in 45% of PCLD patients without proof of malignancy. CA19-9 is produced by cyst epithelium, and as a consequence high CA19-9 levels are present in cyst fluid.[27] Other tumor markers such as CA-125, CEA, and alpha-fetoprotein may be elevated, although not in the range of CA19-9.[28-30]

Surgical Options

The principle aim of treatment of PLD is to reduce symptoms by decreasing liver volume. Options for the management include conservative management, invasive, or medical measures.

Aspiration and Sclerotherapy. Aspiration-sclerotherapy involves aspiration of a cyst followed by injection of a sclerosing agent that causes destruction of the epithelial lining inhibiting fluid production.[31,32] The main indication for aspiration-sclerotherapy is a large symptomatic liver cyst. In PLD it is best to select a dominant cyst that is likely to be responsible for the symptoms, usually the largest cyst (Figs. 1, 2). Most commonly, cysts with a diameter of >5 cm are good candidates for therapy. The technique involves puncture of the cyst with a 5 or 7 French catheter with an aspiration needle.[33] After aspiration of the total content of the cyst, a sclerosing agent is injected and left in the cyst for a predetermined time (Supporting Information Table 1). In general, hepatic cysts do not communicate with the biliary tree. The value of routine use of contrast media remains to be determined. The most commonly used sclerosing agent is ethanol, but minocycline and tetracycline are also used. These latter agents destroy the cyst wall by the low pH that is created in the cyst.[34,35] The volume of ethanol used varies from 10% to 25% of the volume of aspirated cyst fluid (Fig. 3).

A literature review revealed 34 articles on 292 patients who had either solitary (50%) or multiple (50%) cysts. The main indications were pain or discomfort of the abdomen, abdominal mass, fullness, and early satiety. The diameter of the treated cysts was between 5 and 20 cm. The procedure was mostly performed in a single session, but some protocols used repeated procedures on consecutive days.[36]

The most common complication was pain during ethanol instillation, which was probably due to peritoneal irritation. The needle or catheter used did not influence outcome, nor did the duration of alcohol exposure. Cysts totally regressed in 22%, whereas partial regression occurred in 19%. Some 21% had recurrence of the treated cysts during follow-up, although most of these patients were free of symptoms. In the majority of patients, symptoms totally disappeared or a reduction of symptoms occurred (Supporting Table 1).

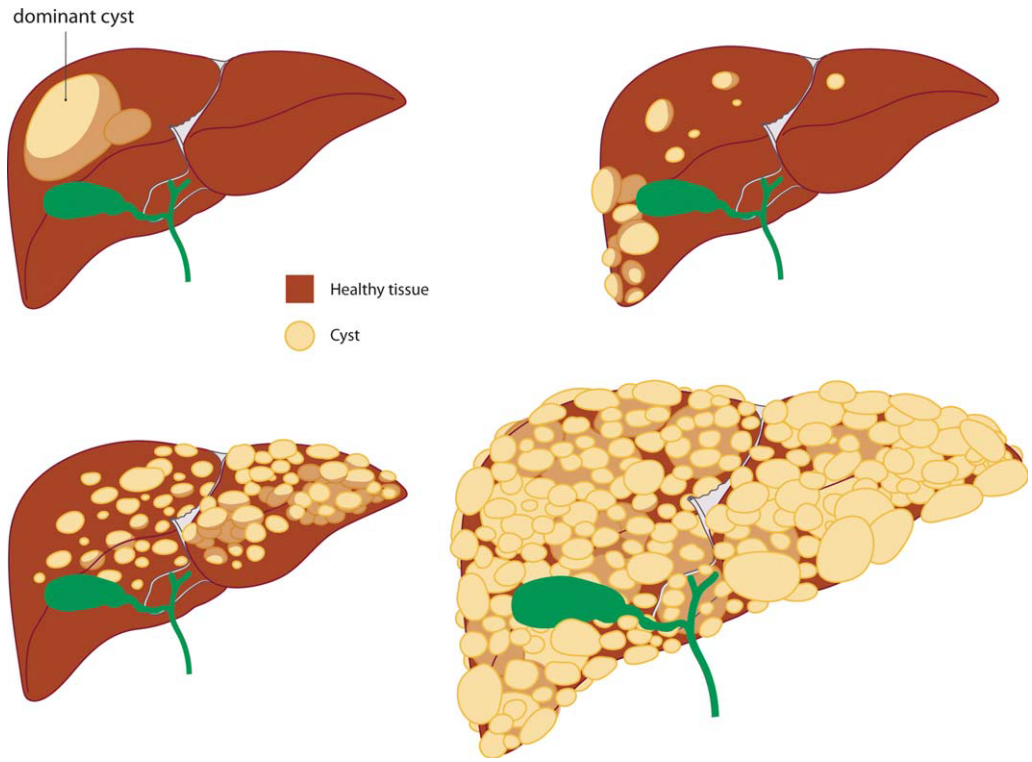

Fig. 1. The cystic liver can be roughly divided into four types: 1. the liver with one or a few dominant cysts; 2. the liver with multiple cysts, clustered and limited to one part of the liver; 3. the polycystic liver that has cysts spread through several segments of the liver, but there are still some segments that are relatively free from cysts; 4. the extensive polycystic liver, that has cysts scattered throughout the whole liver, with hardly any normal, recognizable liver parenchyma left.

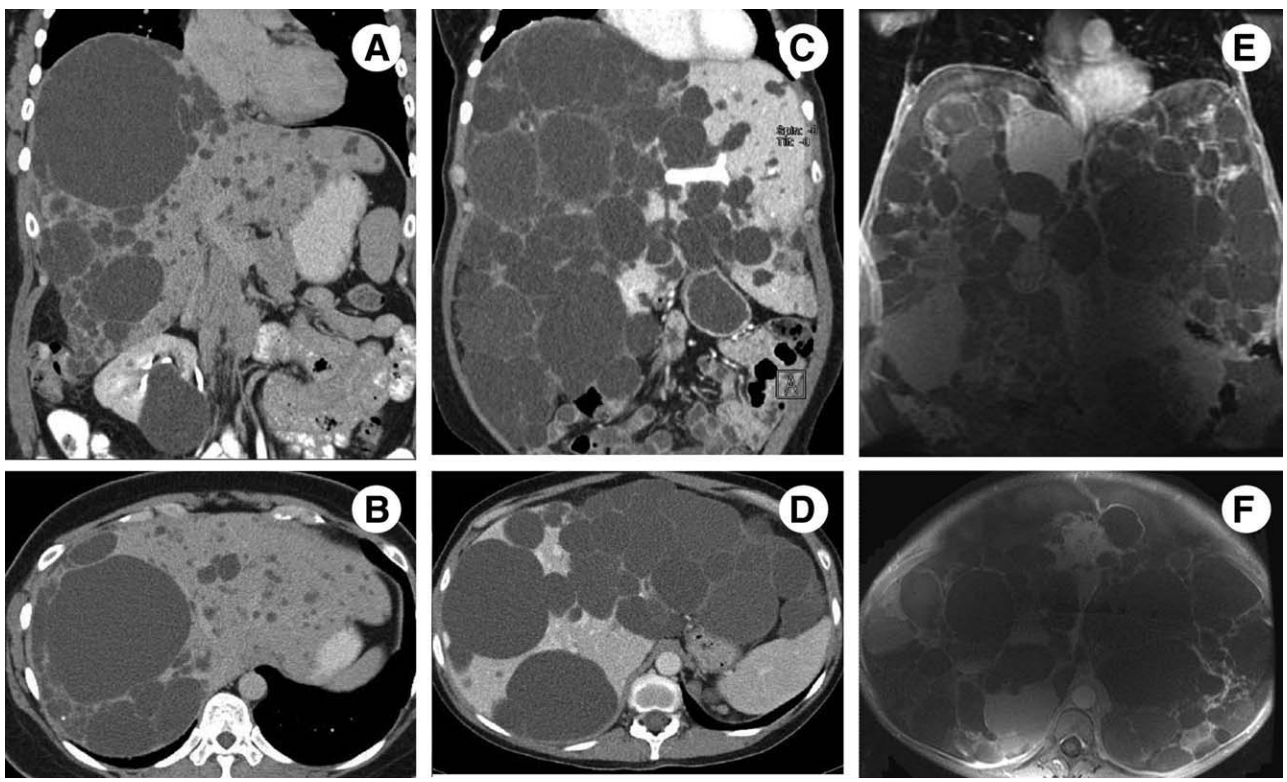

Fig. 2. Various types of (poly)cystic liver. (A,B) Coronal and axial CT images showing a symptomatic dominant cyst best treated by percutaneous aspiration and alcohol sclerosis. (C) Coronal CT image demonstrating severe symptomatic cystic liver disease with relative sparing of the left lobe best treated by combined right hepatectomy/cyst fenestration. (D) Axial CT image demonstrating severe symptomatic cystic liver disease with relative sparing of the right lobe best treated by combined left hepatectomy/cyst fenestration. (E,F) Coronal and axial MR images illustrating severe symptomatic cystic liver disease treatable only by liver transplantation.

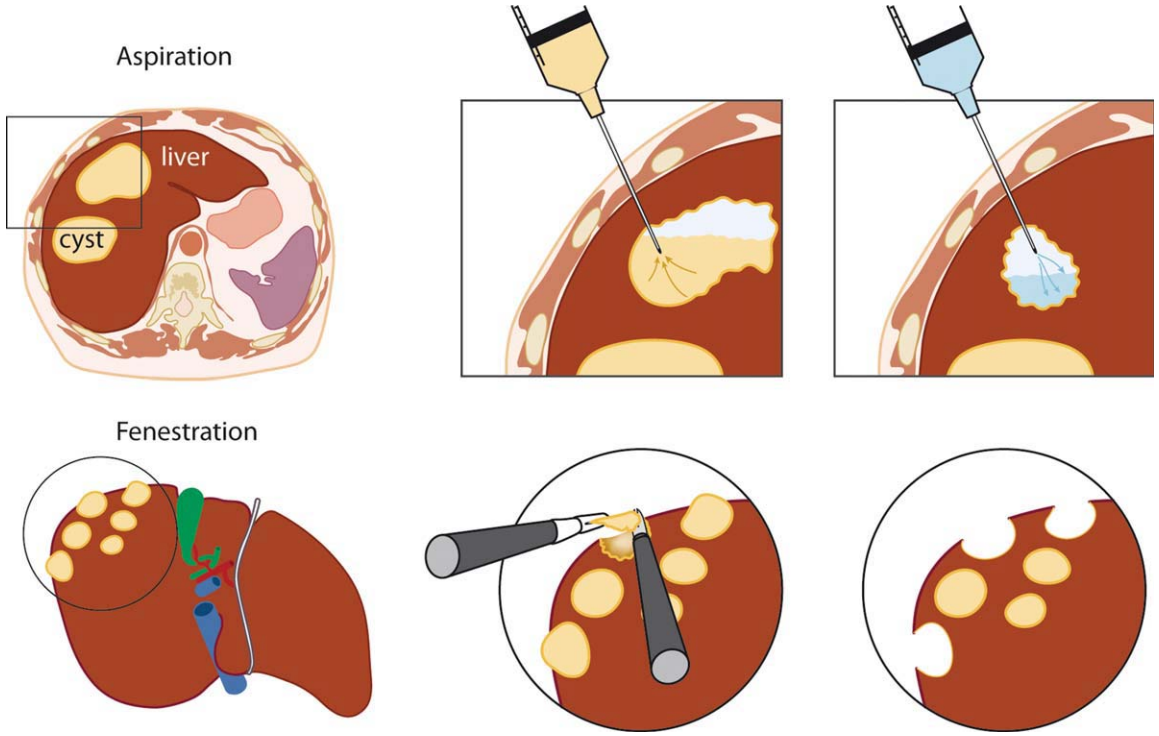

Fig. 3. Radiological and surgical options for polycystic liver. This figure highlights the two most commonly used invasive therapies for polycystic liver. Aspiration: The left panel shows a transverse view of a liver with two large cysts. The middle panel depicts aspiration of the largest cyst. The right panel demonstrates the injection of a sclerosing agent. Fenestration: The left panel shows a liver with a complex of multiple cysts. This makes the cysts amendable to laparoscopic fenestration where the cysts are incised (middle panel) resulting in loss of cystic volume (right panel).

Fenestration. Fenestration is a technique that combines aspiration and surgical deroofing of the cyst in a single procedure (Fig. 3). Surgical access has the advantage that multiple cysts can be treated at once during the procedure. With laparoscopy the view of the cranially located liver segments is limited; therefore, patients with cysts in segments VII-VIII, the upper part of the liver, are not ideal candidates for this procedure.[37,38]

We traced 43 articles on surgical fenestration in 311 PLD patients. Prior to 1994 the fenestration procedures were performed with laparotomy, whereas after 1994 the initial approach became mainly laparoscopic (80% versus 20% laparotomy). Only 22% of laparoscopic procedures needed conversion to an open approach, mainly because of technical reasons or uncontrolled bleeding (Supporting Information Table 2).

In 92% of cases, immediate symptom relief was achieved, but on follow-up 24% of cyst recurred and symptoms recurred in 22%. Reoperation was required for management for the majority of patients with recurrences. Mean hospital stay in most patients was about 4 days and ranged between 1-19 days. Hospital stay was longer for patients who underwent open surgery. One series compared complication rates after laparoscopic and laparotomic approach, and found that the latter procedure led to higher morbidity rates (29 versus 40%).[39]

Main complications of fenestration were ascites, pleural effusion, arterial or venous bleeding, and biliary leakage. Overall morbidity in these patients was 23%. Mortality was 2% and the causes of death were irreversible shock, hepatic abscesses, and acute renal failure (Supporting Information Table 2).

Factors that predicted failure of the procedure were previous abdominal surgical procedures, deep-seated cysts, incomplete deroofing technique, location of cysts in segments VII-VIII, and the presence of diffuse PLD. In the latter situation conversion to laparotomy was more likely to be successful. Widely fenestrated cysts were less likely to recur than cysts that have received a smaller window.[40]

Segmental Hepatic Resection. Segmental hepatic resection may be considered in patients who harbor cyst rich segments, but have at least one segment with predominantly normal liver parenchyma (Fig. 1). Hepatic resection is usually reserved for patients with massive hepatomegaly. Although this procedure was first described in the early 1980s,[41] few centers gained extensive experience with this procedure and the

collective literature describes the clinical experience of fewer than 340 patients (Supporting Information Table 3).

Most surgeons start with the sequential fenestration of easily accessible cysts followed by resection of major cyst segments and extensive fenestration of residual cysts. The extent of the resection depends on the distribution and location of cysts and ranges from a single segment to an extended lobectomy. A remnant of 25%-30% of the expected normal liver parenchyma has been suggested for a good postresectional outcome.[42]

Resection is considered when fenestration alone is unlikely to significantly reduce liver volume and when liver transplantation is unwarranted. It is suitable for patients who are significantly incapacitated by their disease and suffer from severe symptoms due to the massive volume of the polycystic liver.

The distortion of the intrahepatic vasculature and biliary system by cysts is a potential source of complications and accurate definition of these structures preoperatively remains difficult, even with current imaging modalities. Moreover, with the unusual large size of the polycystic liver, the liver is rigid and limits its mobility. Although the hilar vessels are easily accessed, the hepatic veins are particularly difficult to access. These factors increase the risk of a venous bleed or bile leakage. Another drawback of hepatic resection is the risk of subsequent adhesions, which may complicate future liver transplantation.

We found 26 articles on 337 PLD patients. Morbidity occurred in 51% of patients and included ascites, pleural effusion, biliary leakage, and hemorrhage. Morbidity was higher in patients who underwent previous surgery or who were on immunosuppressive drugs. Mortality was 3%, and causes of death were intracerebral hemorrhage, septic shock, and Budd-Chiari syndrome. Mean hospital stay was about 10-15 days. Reoperation was performed because of persistent bleeding, thrombosis, or biliary leakage. The complication rate depended on experience and was lower in high-volume centers. Symptom relief was achieved in 86%. Cyst recurrence was seen in 34% of all patients (Supporting Information Table 3). However, the immediate improvement in patients after the postoperative period was significant.

Liver Transplantation. Liver transplantation is the only curative therapeutic option in patients with severe polycystic liver.[3] Transplantation is indicated in those patients with extremely disabling symptoms that lead to a seriously decreased quality of life. In addition, untreatable complications, such as portal hypertension and nutritional compromise, are indications for liver transplantation. Liver transplantation as a therapeutic option should be weighed carefully in view of the shortage of liver donors, the fact that PLD is not associated with excess liver-related mortality, and that liver synthetic function remains normal even in advanced cases.

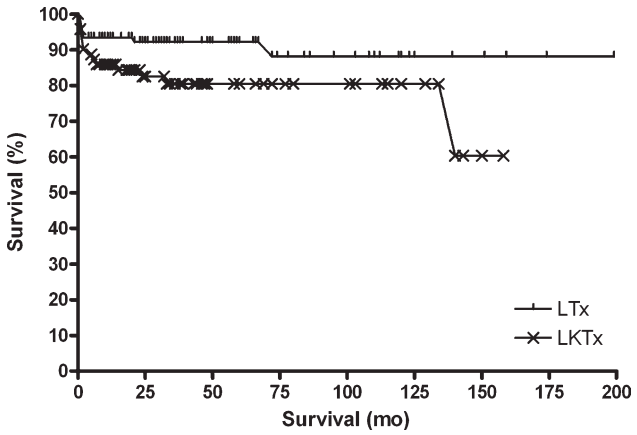

Fig. 4. Survival after liver transplantation.

There were 29 articles on 206 PLD patients. The main indications for transplantation were abdominal pain, distension, fullness, dyspnea, extreme fatigue, and malnutrition. Overall, quality of life was severely impaired and patients were physically and socially disabled by these symptoms. A significant proportion of procedures (42%) were a combined liver and kidney transplant. Morbidity was seen in 83 of all patients (41%), whereas 30-day mortality was 5% and overall mortality 17% (Supporting Information Table 4). When we divided patients according to whether the procedure included a kidney transplantation or not, the 1- and 5-year survival in the patients with liver transplantation alone was 93% and 92%, whereas patients who received a combined liver and kidney transplantation had a 1- and 5-year survival of 86% and 80%, respectively (Fig. 4). Retransplantation of the liver was necessary in six patients (3%). Quality of life improved in almost all patients.

The higher survival rates with liver transplantation alone are higher compared to combined liver and kidney transplantation, and may be due to the more extensive abdominal surgery, as well as renal insufficiency in patients requiring the combined procedure. Combined transplantation using a liver and kidney from the same donor protects the kidney graft from rejection and improves kidney graft survival.[43,44] Combined liver and kidney transplantation should only be performed in patients with advanced renal insufficiency or on dialysis.

Medical Options

Somatostatin Analogs. One of the potential factors in promoting cyst growth is cAMP. Secretin, the major cAMP agonist in cholangiocytes, stimulates the targeting and insertion of several transporters and channels into the apical membrane of cholangiocytes. Biliary epithelia maintain a cAMP-dependent Cl and HCO3 secretion that facilitates fluid secretion.[45,46] Intravenous administration of secretin in ADPKD patients increased fluid secretion in hepatic cysts.[47] This suggests that increased cAMP drives fluid secretion in hepatic cysts. Somatostatin analogs are cAMP level inhibitors and decrease fluid secretion and cell proliferation in many cell types, including cholangiocytes,[18,48-51] thereby providing a novel opportunity to modulate cystogenesis. The basic concept is that cyst growth is regulated by a continuous process of secretion and reabsorption. Inhibition of secretion by somatostatin analogs may ultimately result in shrinking of hepatic cysts. The first experiments in humans with massively polycystic livers in the early 1990s failed to demonstrate any decrease in hepatic cyst growth or size following octreotide administration.[52] The techniques used to evaluate liver volume were not sensitive enough to detect small but significant differences.

In the pck (PKHD1, fibrocystin) rat model of autosomal recessive PLD,[53] cAMP concentrations in cholangiocytes were 2 times higher than in unaffected rats. In vivo, octreotide lowered cAMP content in cholangiocytes and serum and inhibited hepatic disease progression, leading to reductions in liver weight and cyst volume. This study provided a strong rationale for the potential value of octreotide in the treatment of PLD. A clinical observation in two patients suggested that a 3- to 6-month treatment with somatostatin analogs dramatically decreased liver volume by 15%-38%.[54]

These developments led to a number of randomized clinical trials that evaluated the effect of long-acting somatostatin analogs in PLD (Fig. 5). The first trial evaluated the effect of lanreotide 120 mg given monthly for 6 months in 54 PLD patients (32 ADPKD; 22 PCLD). The primary endpoint was change in total liver volume assessed by computed tomography (CT). The mean liver volume decreased 2.9% with lanreotide compared to an increase of 1.6% in the placebo group.[4] A randomized, double-blind clinical trial treated 42 patients (36 ADPKD; 6 PCLD) with monthly injections of long-acting octreotide 40 mg for 1 year. Liver volume assessed by magnetic resonance imaging (MRI) decreased by 4.9% with octreotide and increased by 0.9% with placebo.[5]

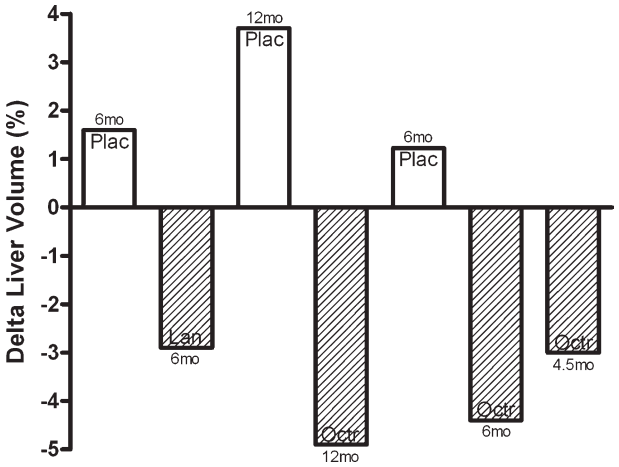

Fig. 5. Percent change of liver volume during treatment with somatostatin analogs or placebo. This figure shows the results of four clinical trials using somatostatin analogs. The first two bars show that 6 months of lanreotide reduces liver volume with 2.9%, whereas liver volume keeps increasing (1.6%) during placebo.[4] The following two bars show that 12 months of octreotide gives a reduction of liver volume (−4.9%), but liver volume increases (3.7%) during placebo.[5] The fifth and sixth bar show that 6 months of octreotide give a reduction of liver volume of 4.0%, whereas it increases with 1.2% on placebo.[6] The last bar shows the results of a trial with octreotide given for 4.5 months. Liver volume reduces with 3.0%. A placebo group is missing.[55]

These results are in line with a post-hoc analysis of a crossover study that treated 12 ADPKD patients with polycystic livers for 6 months with long-acting octreotide LAR 40 mg each month. Liver volume decreased by 4.4% during octreotide administration, whereas it increased by 1.2% with placebo.[6] The volume-reducing effect of octreotide is not dependent on its formulation. Short-acting octreotide administered at a dose of 100 μg three times daily subcutaneously for 70-180 days in eight patients (seven ADPKD; one PCLD) resulted in a median reduction of liver volume by 3.0%[55] (Fig. 5).

The randomized clinical studies documented that the beneficial effect of somatostatin analogs was associated with improved general health perception.[4,5] Somatostatin analogs are well tolerated. Side effects such as diarrhea and abdominal cramps occur after the first injections but disappear after prolonged use.

mTOR Inhibitors. Another medical option that has gained popularity are mammalian target of rapamycin (mTOR) inhibitors. This class of drugs has strong antiproliferative effects and has become an integral part of immunosuppressive therapy after solid organ transplantation.[56] mTOR is upregulated in animal models of polycystic kidney disease and inhibition slows disease progression.[57,58] In a trial with 16 ADPKD patients who had polycystic livers after renal transplantation the mTOR inhibitor sirolimus reduced

liver volume by 11.9% when given for an average of 19.4 months, whereas tacrolimus caused an increase of 14.2%.[19]

There are still many outstanding questions. It is unknown why some patients respond well, whereas others do not, but it appears that larger livers respond better to treatment than smaller livers.[4] The most important issue is whether the beneficial effect is maintained with prolonged therapy. Answers might come from ongoing trials that evaluate the effect of a 3-year treatment.[6] Finally, whereas somatostatin analogs are well tolerated, the side-effect profile is less acceptable with mTOR inhibitors.[59,60]

Conclusion

PLD is a progressive disease, and a substantial minority of patients will develop severe symptoms. Invasive procedures may provide relief through liver volume reduction in selected cases. Apart from liver transplantation, none of the currently available options have been shown to change the natural course of the disease. In addition, there is no consensus on the optimal timing or optimal procedure to be carried out. Although all procedures listed here are technically feasible, they do carry the risk of considerable morbidity, and potential benefits should be weighed carefully against the drawbacks of the individual procedures. Recent clinical trials have shown that it is possible to reduce liver volume with octreotide or lanreotide. We expect a surge in clinical trials evaluating medical therapy in PLD in the coming years. We have to bear in mind that the costs of these treatments are considerable. In the Netherlands, 1 injection with 40 mg octreotide LAR costs € 2092 ($2940), while the costs for 1 injection longacting lanreotide (120 mg) are € 1983 ($2787).

Future directions include identifying other targets and determining whether a combination of drugs which act on different pathways may have a synergistic effect on volume reduction. Given the modest effect of the drugs in clinical trials, the uncertainty as to who will respond, how long treatment should continue, and the expense involved, it is clear that the somatostatin analogs should not be used outside of clinical trials.

It is paramount that future studies in this field use consistent selection criteria and define their outcome measures. The field is in clear need of studies that determine efficacy of the various therapeutic options in terms of objective symptom relief and/or reduction in liver volume measured by CT or MRI. Ultimately these efforts should lead to a clearer understanding of the efficacy of therapeutic options so that the treatment recommendations may be individualized.

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