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Polycystic Liver Disease: The benefits of targeting cAMP

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Polycystic Liver Disease (PLD), a group of genetic disorders, exists alone as Autosomal Dominant PLD or in association with Autosomal Dominant or Recessive Polycystic Kidney Disease (ARPKD and ADPKD, respectively). PLD is characterized by the presence of fluid-filled liver cysts derived from cholangiocytes as a result of mutations in PLD-related genes. Hepatic cystogenesis worsens over time increasing liver volume by 0.9–1.6% per year. The continuous progression of PLD can result in hepatomegaly with total liver volumes exceeding 10 L. Patients with severe disease have constant abdominal pain and distension, dyspnea, gasrtroesophageal reflux, back pain and hepatic and portal vein compression.[1]

Multiple in-depth pre-clinical studies showed that many intracellular signaling pathways and cellular functions are dysregulated in PLD. Indeed, hepatic cystogenesis has been associated with: (i) enhanced fluid secretion into the cyst lumen; (ii) increased rates of cholangiocyte proliferation; (iii) structural and functional ciliary abnormalities; (iv) abnormal cell-extracellular matrix interactions; (v) impaired cell cycle progression; (vi) morphological centrosomal defects; (vii) global changes in mRNA, microRNA and protein expression; and (viii) increased levels of intracellular cAMP.[2] Experimental evidence suggests that cAMP controls different mechanisms in PLD including cell proliferation and fluid secretion. Indeed, intravenous administration of secretin, a major agonist of cAMP signaling in cholangiocytes via interaction with the basolaterally located secretin receptor, increases fluid secretion in hepatic cysts of ADPKD patients.[3] In cultured cystic cholangiocytes isolated from an animal model of ARPKD, the PCK rat, and from patients with ADPKD, elevated cAMP enhances cell proliferation, accelerates fluid secretion and affects cell cycle progression via its down-stream modulators PKA, EPAC and ERK1/2/MEK.[2, 4, 5] Together, these observations suggest an important role for cAMP machinery in PLD implicating elevated cAMP as a potential therapeutic target.

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Somatostatin and its synthetic analogs (such as octreotide and pasireotide), by binding to somatostatin receptors (SSTRs), inhibit cAMP production in different cell types including cholangiocytes. Suppression of cAMP is triggered in response to activation of any of five known SSTRs, while inhibition of cell proliferation occurs predominantly via SSTR2 and SSTR5 and, in some cases, SSTR1 and SSTR3.[6] All five SSTRs are present in rat and human cholangiocytes and decreased levels of SSTR1 and SSTR2 (but not SSTR3 and SSTR5) has been observed in liver cysts.[6] Experimental *in vitro* models of hepatic cystogenesis have demonstrated that enhanced cholangiocyte proliferation and increased fluid secretion were abolished after treatment with somatostatin analogs.[4, 6, 7] Attenuated hepatic cystogenesis and decreased fibrotic scores were also observed in several animal models of PLD in response to cAMP inhibition by octreotide and pasireotide. Importantly, repressed cystogenesis was accompanied by reduced cAMP levels in serum and in freshly isolated cholangiocytes from octreotide-treated PCK rats.[6, 7]

In line with these preclinical studies, several case-reports supported the use of somatostatin analog therapy in PLD. Total liver volume was reduced after 3 and 6 months of treatment with octreotide by 14.9% and 38.3% in two patients with PLD, respectively.[8] In an ADPKD patient who received lanreotide for 6 month, total liver volume was decreased by 10%.[9] Another case-report documented 6.3% reduction in total liver volume after 12 months of octreotide therapy.[10] Finally, in a larger case series (8 patients treated with short-acting octreotide for 135 days), a 3% decrease in liver volume was described.[11]

Together, the pre-clinical findings and several case-reports set the stage for a number of randomized clinical trials to examine the efficacy of long-acting release somatostatin analogs (octreotideLAR and lanreotide) in patients with PLD.

In the current issue of *Clinical Gastroenterology and Hepatology*, Pisani and colleagues evaluated the effects of octreotideLAR therapy on total liver volume in patients with relatively mild PLD in a three-year prospective, randomized, placebo-controlled trial followed by a two-year recovery period. Patients were divided into octreotideLAR treated (n=14) and placebo-treated (n=13) groups. In the octreotideLAR group, total liver volume was decreased by 130.2±133.2 ml (i.e., 7.8±7.4%; p=0.003) over the three-year treatment period while in placebo group an increase of 144.3±316.8 ml (i.e., 6.1±14.1%; p=0.0002) was observed. At the end of treatment, total liver volume was 357.7±619.9 ml smaller in patients receiving octreotideLAR compared to controls. During the two-year recovery, total liver volume increased in octreotideLAR group by 115.8±127.4 ml (9.7±0.2 %) and by 80.1±90.0 ml (4.9±7.2%) in patients originally randomized to placebo. Despite the liver re-growth during off treatment, over the five years of observation total liver volume in octreotideLAR patients was decreased by 14.4±138.4 ml (0.8±9.7%) but increased by 224.4±331.7ml (11.0±14.4%) in those on placebo. Overall, by the end of 5-year period, total liver volume was 322.1±604.9 ml smaller in patients originally randomized to octreotideLAR than in controls. Interestingly, the reduction in total liver volume during treatment and recovery to baseline values after treatment did not correlate with mean baseline liver volume (i.e., below or above the median) in octreotideLAR group. In contrast, in the control arm, liver growth was faster in patients with larger total liver volume than in those with smaller livers.

Besides the study described here, several other clinical trials have tested the effects of somatostatin analogs in PLD (Table 1). Van Kiempema et al reported that twenty seven patients treated with lanreotide for 6 months experienced a reduction of 2.9% in total liver volume while in subjects randomized to placebo (n=27) a 1.6% increase was documented.[12] In the 12 months of open-label study, an overall 4% decrease in total liver volumes was further observed in 41 participants.[13] Caroli et al described a 71±57 ml reduction in total liver volume in response to octreotideLAR in 12 ADPKD patients after 6 month of treatment.[14] Hogan et al randomly allocated 42 patients to octreotideLAR (n=28) or placebo (n=14) treatment for 12 months.[15] As a result, liver growth was decreased by 4.95% in octreotideLAR group compared to 0.9% increase in placebo group. A total of 41 patients participated in open-label extension study for additional 12 months.[16] In subjects initially randomized to placebo, liver volume decreased by 7.66% but was sustained in patients initially treated with octreotide. In pooled analysis, after 12 months of octreotide treatment total liver volume was decline an average by 6.08%. This study was extended again for an additional 24 months after 8.3 month off therapy during which liver growth was increased toward the baseline.[17] Twenty-four patients that underwent two additional years of treatment experienced a reduction of 4.7% per year in total liver volume. Therefore, after 4 years of octreotideLAR therapy, liver growth declined by 11.8%.[17] In addition, two other nonplacebo controlled clinical trials showed beneficial effects of somatostatin analogs in PLD.[18, 19] Thus, based on these studies, it is reasonable to conclude that : (i) treatment with somatostatin analogs for 6–12 months decreases total liver volume; (ii) reduction in liver volume is sustained beyond 12 month of therapy; (iii) response to treatment varies among patients with some (~15%) non responders; (iv) once therapy is stopped, liver volume starts to increase toward baseline suggesting that long term continuous or intermittent treatment is required; (vi) somatostatin analogs are well tolerated and improve quality of life; and (vii) similar changes in liver volume in response to treatment occurs in patients with ADPKD-associated PLD or isolated ADPLD.

To date two somatostatin analogs, octreotide and lanreotide, have been used in clinical trials. A dose of 120 mg of lanreotide is equivalent to 60 mg of octreotide.[15] Current somatostatin analogues target mainly SSTR2, the expression of which appears to be decreased in hepatic cysts.[6] Another somatostatin analog, pasireotide, has high affinity to four SSTRs, with IC_{50} of 9.3 nM (SSTR1), 1.0 nM (SSTR2), 1.5 nM (SSTR3) and 0.16 nM (SSTR5). Pasireotide is more stable (i.e., 12 hour half-life) than octreotide (i.e., 70–113 min). Therefore, pasireotide might be promising therapy for patients that did not respond to octreotide treatment. A comparative pre-clinical study demonstrated that pasireotide suppresses hepatic and renal cystogenesis more efficiently than octreotide.[6] A clinical trial assessing the efficacy of pasireotide is now underway at Mayo Clinic.

The clinical trial published in current issue of *Clinical Gastroenterology and Hepatology* is one more in the line of several others that described the efficacy of somatostatin analogs in PLD. How does this study differ from previously reported? As shown in Table 1, all[12, 13, 15–19] (but one[14]) clinical studies involved patients with severe polycystic liver disease (median total liver volumes range: 4606 ml – 6476 ml). Patients included in the trial conducted by Pisani and colleagues had relatively small median liver volumes at baseline (i.e., 1477 ml in octreotideLAR group and 1637 ml in placebo group). Despite earlier

observations that patients with very enlarged livers respond to treatment more efficiently than those with smaller livers,[15] a substantial reduction of 7.8% in total liver volumes was detected in response to octreotideLAR therapy in patients with relatively small livers. This observation suggests that while clinical symptoms are the basis for the enrollment in clinical trials, baseline liver volume might also be taken to consideration.

Moreover during 2 years off therapy, the liver volumes continued to decrease in octreotideLAR patients as compared to the placebo group suggesting that early intervention might not only halt the growth of liver cysts but even reduce subsequent rate of liver cystogenesis. Finally, given that somatostatin analogs for PLD treatment are not approved by FDA and therapy is expensive (i.e., $7,000–$11,000 per month for patients with health insurance who have to obtain pre-approval usually on a case by case basis) it may be reasonable to consider an on/off therapy regimen; this is perhaps the major implication of the work by Pisani and colleagues. In conclusion, this study demonstrated that treatment of PLD at early stages might not only stabilize but may consistently reduce total liver volume preventing further suffering. However, an extended study with a larger number of patients in order to detect the long-term beneficial efficacy and safety profiles of somatostatin analogs, as well as the utility of an on-off approach, is necessary.

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Table 1

Studies evaluating somatostatin analogs in PLD

Drug	Treatment duration	Patients	TLV (ml) Placebo group:			TLV (ml) Treatment group			Ref
			Baseline	after treatment	change	Baseline	after treatment	change	
Lanreotide (120 mg)	6 month	54	4689	4895	1.6%	4606	4471	−2.9%	12
	12 month (OLE)	41	-			4974	4711	−4.0%	13
	Note: after 6 month **off treatment**, TLV increases by 4% toward baseline								
Octreotide (40 mg)	6 month	12	1580	1594	0.9%	1595	1524	−4.5%	14
Octreotide (40 mg)	6 month	42	5374	5361	0.92%	5907	5628	−5.0%	15 16 17
	12 month (OLE)	41	Patients received octreotide after 12 month of placebo				5649	−0.77%	
			5360	4952	−7.7%				
	Note: pooled data in patients received octreotide (for 12 or 24 month) show 6.8% overall reduction in TLV								
	24 month (OLE	28	-			5863	5617*	−4.7%	
							5304**		
	Note: ** - reduction in TLV after 12 month of treatment; ** - reduction in TLV after 24 month of treatment. After 8.3 month **off treatment**, TLV increased by 4% toward baseline. Over 4 year period of treatment, TLV was reduced by 11.8%.								
Octreotide (40 mg)	48 weeks	23	No placebo group			6476	5751	−3.5%	19
			Note: in this trial combinational effect of octreotide and everolimus was assessed. Result of mono-therapy (i.e., octreotide only) was included in this table.						
Lanreotide (90 mg)	6 month	53	No placebo group			5244	5121		18
	12 month		Note: after 6 month of treatment Lanreotide dose was increased to 120 mg in non-responders for additional 12 month of treatment						