Liver Disease in ADPKD
WEBINAR, July 13th 2010.

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Assistant Professor, Division of Nephrology & Hypertension,
Mayo Clinic, Rochester, MN.
Outline

• Historical
• Natural History
• How do you get liver cysts?
• Symptoms
• Medical management
• Surgical management
• New treatments
<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPKD</td>
<td>PKD1</td>
<td>16p13.3</td>
<td>Polycystin 1</td>
<td>Membrane receptor</td>
</tr>
<tr>
<td></td>
<td>PKD2</td>
<td>4q21-23</td>
<td>Polycystin 2</td>
<td>Calcium channel</td>
</tr>
<tr>
<td>ADPLD</td>
<td>PLD1</td>
<td>19p13.2</td>
<td>Glucosidase II</td>
<td>ER protein processing</td>
</tr>
<tr>
<td></td>
<td>PLD2</td>
<td>6</td>
<td>SEC63</td>
<td>ER protein processing</td>
</tr>
</tbody>
</table>
Cystogenesis in ADPKD/ADPLD

Normal

PLD

Intralobular ductule

Interlobular duct

Area duct

Segment duct

Right hepatic duct

Common hepatic duct

Common bile duct
Prevalence of Liver Cysts in the General Population

![Bar chart showing the prevalence of liver cysts across different age groups. The x-axis represents age in years (20, 40, 60, 80, >80), and the y-axis represents the percentage (%). The chart indicates a rise in prevalence with age, with a significant increase in individuals over 80 years old.]
MRI Evaluation of Hepatic Cysts in Early ADPKD: CRISP Cohort.

Kyongtae T. Bae,* Fang Zhu,* Arlene B. Chapman,† Vicente E. Torres,‡ Jared J. Grantham,‖ Lisa M. Guay-Woodford,§ Deborah A. Baumgarten,† Bernard F. King, Jr.,‡ Louis H. Wetzel,‖ Philip J. Kenney,§ Marijn E. Brummer,† William M. Bennett,‖ Saulo Klahr,* Catherine M. Meyers,† Xiaoling Zhang,** Paul A. Thompson,** J. Philip Miller,** and the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)

*Departments of Radiology, Medicine, and **Division of Biostatistics, Washington University, St. Louis, Missouri; †Emory University School of Medicine, Atlanta, Georgia; ‡Mayo Foundation, Rochester, Minnesota; §Departments of Medicine (Renal Division) and Radiology, University of Alabama at Birmingham, Birmingham, Alabama; ‖University of Kansas Medical Center, Kansas City, Missouri; §Northwest Renal Clinic, Portland, Oregon; and *National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

- **Quantitative MRI scans:** 3mm slices
- **Prevalence of liver cysts in early ADPKD**
  - 58% in 15-24yo
  - 85% in 25-34yo
  - 94% in 35-46yos

**T2-weighted MRI From Four Different Patients With Variable Severity Of Hepatic And Renal Cysts**

- **24yo man** liver cysts (6.3ml) renal cysts (15.4 ml).
- **46yo man** mild hepatic cyst (9.3 ml) severe renal cysts (1940 ml).
- **44yo man** hepatic cysts (318.7 ml) but mild renal cyst burden (37.6 ml).
- **30yo woman** hepatic cysts (2368.8 ml) and renal cysts (1084.5 ml).

Bae, K. T. et al. CJASN 2006;1:64-69
Symptomatic Polycystic Liver Disease (1)

Mass Effect (by dominant cyst/massive PLD)
- Abdominal distension/pain
- Early satiety, heartburn, emesis
- Malnutrition, loss of muscle/fat
- Dyspnea, orthopnea
- Change in bowel pattern, hemorrhoids
- Back pain
- Hernias, uterine prolapse, rib fractures
- Venous obstruction (hepatic, IVC, porta)
- Bile duct obstruction
Symptomatic Polycystic Liver Disease

Complications
– Hemorrhage
– Rupture
– Infection

Rare Associations
– Bile duct dilatation
– Congenital hepatic fibrosis
– Cholangiocarcinoma
Liver Cyst Infection

• Risk Factors
  – Recent abdominal surgery
  – Kidney Transplant
  – Chronic dialysis

• Symptoms
  – Fever + new onset RUQ pain
  – Leukocytosis ↑ESR
  – ↑ALP
  – Bacteremia
  – Cultures of undrained cyst fluid +ve
Symptomatic Polycystic Liver Disease

Nonsurgical Treatment Options

• Avoid estrogens

• Avoid caffeine
  • Caffeine stimulates cAMP

• $\text{H}_2$-blocker or $\text{H}^+/$$\text{K}^+$ ATPase inhibitor
  • ↓ secretion rates from unroofed liver cysts, possibly by inhibiting gastric acidity and secretion of secretin

• Somatostatin analogues
  • Long-acting octreotide/ lanreotide
Symptomatic Polycystic Liver Disease
Surgical Treatment Options

1. Percutaneous aspiration/sclerosis
2. Fenestration (laparoscopic or open)
3. Hepatic resection/fenestration
4. Liver transplantation
Symptomatic Polycystic Liver Disease
Autosomal Dominant Polycystic Liver Disease: Alcohol Sclerosis of Liver Cysts

Success rate:
- Primary: 69%
- Secondary: 23%
- Failure: 8%

Complications:
- Major: None
- Minor: Transient pain
Autosomal Dominant Polycystic Liver Disease
Laparoscopic Fenestration For Polycystic Liver

INTRAOPERATIVE COMPLICATIONS
Hypothermia
Hypercapnia

POSTOPERATIVE COMPLICATIONS
Transient ascites (46%)

SYMPTOMATIC RELIEF
85%

RECURRENCE of SYMPTOMS
73%
Useful for few large cysts

Kabbej Brit J Surgery 83:1697, 1996
Massive Polycystic Liver Disease

- Focal (preserved liver segments in >80% of patients)
- Parenchymal volume constant

Everson et al: Hepatology 8:1627, 1988
Resection-Fenestration for Polycystic Liver Disease
Distribution of Segmental Resection

Segments

0 20 40 60 80 100
1 2 3 4 5 6 7 8

Segments

1 2 3 4 5 6 7 8

- Performance status normalized or improved in 75% of patients and 73% returned to work full-time.
- At follow-up, health survey scores were similar to the general population despite subsequent recurrence of symptoms in 73% of patients.

Schnelldorfer et al.

*Annals of Surgery* • Volume 250, Number 1, July 2009
Massive Polycystic Liver Disease
Combined Resection-Fenestration
Liver Transplantation for Massive Polycystic Liver Disease
Model for End-Stage Liver Disease (MELD)

Numerical system that ranks (from 6 to 40) patients waiting for a liver based on three lab test results:

- Bilirubin (how effectively the liver excretes bile)
- INR (prothrombin time, ability to clot blood)
- Creatinine (kidney function)
Liver & Kidney Transplantation for PLD

- First done 1988
- Malnutrition and failure to thrive

  - MELD = 15 7.5
  - Liver weight 2.6–12.6 kg

- 5-year survival for liver transplant considering all published studies ~ 85%
- Excellent Quality of Life
- Most of the mortality occurring in the first 3 months.

T Ueno. Transplantation. 82 (4) 501-7. 2006
51yo (59kg) With ADPKD With A 9.1-kg Liver Underwent Liver Transplant
Symptomatic Polycystic Liver Disease

Alternative Treatment Options

- Hepatic artery embolization
- Endovascular stent
- Transjugular intrahepatic portosystemic shunt (TIPS)
- La Veen shunt
Severe Polycystic Liver Disease
Hepatic Artery Embolization

Ubara. AJKD 43: 733, 2004
Severe Polycystic Liver Disease

Hepatic Artery Embolization

Pre

Post (2 years)

Ubara. AJKD 43: 733, 2004
POLYCYSTIC LIVER DISEASE
STENTING for INFerior VENA CAVA OBSTRUCTION
Aspiration and alcohol sclerosis

Laparoscopic fenestration

Hepatic artery Embolization

Before right lobectomy & Cyst Fenestration

After right lobectomy & Cyst Fenestration

Liver Transplant

www.pkdcure.org
Symptomatic Polycystic Liver Disease

Nonsurgical Treatment Options

- Avoid estrogens, caffeine
- H2-blocker or H+/K+ ATPase inhibitor
- Somatostatin analogues
- Sirolimus (?)
Mechanisms of Cyst Development:

- Defective cell planar polarity
- Centrosomal amplification
- Cell cycle dysregulation
- Increased apoptosis
- Increased fluid secretion
- Increased cell proliferation

Mutations in ADPKD (
*PKD1* and *PKD2*)

Mutations in ADPLD (*PRKCSH* and *SEC63*)

- cAMP elevation
In Cholangiocytes, cAMP Facilitates Fluid Secretion & Proliferation

**Basolateral** (blood)

- Somatostatin

**Apical** (bile)

- Secretin

- **[↓cAMP]**

- Fluid secretion

- Proliferation

- SSTR2
- SSTR3
- SSTR5

**Cyst growth**  

*Masyuk, Gastroenterology, 2007*
**BLOOD**

- **Gastrin**
  - $\Rightarrow$ Na$^+$
- **Secretin**
  - $\Rightarrow$ cAMP
- **Somatostatin**
  - $\Rightarrow$ cAMP

**BILE**

- **HCO$_3^-$**
- **Cl$^-$**

**Pathways:**
- Gastrin + Ca$^{2+}$ + IP$_3$ + PKC$\alpha$ 
- Secretin + PKA 
- Somatostatin + cAMP 
- CFTR Channel Opening

**Reactions:**
- (+) Activation
- (-) Inhibition

**Chemical Structures:**
- Na$^+$
- H$^+$
- HCO$_3^-$
- Cl$^-$
cAMP Targeting Attenuates Hepatic and Renal Cyst Growth in the PCK Rat, an Animal Model of PLD

Masyuk, Gastroenterology, 2007
**Long-Acting Octreotide Trial in ADPKD**

- Randomized, placebo-controlled, cross-over study x 6 months
- Small study (n=12)
- Good safety profile
- Dose adjustments advised for patients with severe renal impairment

TLV ↓1,641±486 to 1,574±469 ml (p<0.005).
\[ \Delta \text{TLV} (-66±56 vs +5±88 ml). \]


Caroli. CJASN. 2010.
LOCKCYSYT STUDY (Lanreotide)

• Lanreotide 120mg x 6 months
• Therapeutic drug levels
• Equivalent to 60mg OctLAR

Table 1: Demographics and baseline clinical characteristics. Data are mean (95% CI).

<table>
<thead>
<tr>
<th></th>
<th>Lanreotide group (N=27)</th>
<th>Placebo group (N=27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.6 (34.4–64.8)</td>
<td>50.3 (32.6–68.1)</td>
<td>0.752</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>3/24</td>
<td>4/23</td>
<td>0.685</td>
</tr>
<tr>
<td>Diagnosis (ADPKD/PCLD)</td>
<td>12/15</td>
<td>20/7</td>
<td>0.027</td>
</tr>
<tr>
<td>Centre (Leuven/Nijmegen)</td>
<td>12/15</td>
<td>12/15</td>
<td>1.000</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.1 (18.7–33.5)</td>
<td>25.7 (18.6–32.8)</td>
<td>0.733</td>
</tr>
<tr>
<td>Liver volume (mL)</td>
<td>4606 (547–8665)</td>
<td>4689 (613–8765)</td>
<td>0.698</td>
</tr>
<tr>
<td>Right and left kidney volume (mL)*</td>
<td>1000 (-39–2039)</td>
<td>1115 (-519–2748)</td>
<td>0.673</td>
</tr>
</tbody>
</table>

*Only ADPKD patients
ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease.

LOCKCYSYT- Results:

- \( \Delta \) Mean LV -2.9\%, 4606 mL (95%CI 547–8665) -> 4471 mL (95%CI 542–8401).
- Placebo group + 1.6%; 4689 mL (95% CI 613–8765) to 4895 mL (95% CI 739–9053) (p<0.01)
- Post-hoc stratification for patients with ADPKD or PCLD - similar changes in liver volume, with significant differences in patients on lanreotide (P<0.01 for both diseases).
LONG-ACTING OCTREOTIDE TRIAL (Mayo Clinic)

Prospective, double blind, placebo controlled (2:1), 42 patients

Octreotide LAR 40 mg IM every 4 weeks

Primary endpoint: % change in liver volume at 12 months (MRI)

Secondary endpoints: % change in kidney and liver/renal cyst volumes

Patient Characteristics

- Age ≥ 18 years
- PLD associated with ADPKD or isolated ADPLD
- Liver volume >4000 mL or symptomatic due to mass effects
- Not a candidate for or declining surgical intervention
- Serum creatinine <3 mg/dL
- Exclusion criteria (pregnancy, major illness, uncontrolled DM)

Open label extension
Study flow diagram

113 Patients were assessed for eligibility

71 Patients Excluded
- Unable to travel to Mayo Clinic
- Liver disease too mild
- Recent liver surgery
- Other pathology considered significant

42 Patients underwent randomization

28 Patients Randomized to receive Oct LAR
- 28 Patients Received Oct LAR
  - 0 lost to follow-up
  - 7 had Protocol violation
  - 7 Decreased to 30mg
  - 4 Decreased to 20mg
  - 3 patients had dose (s) withheld
  - 0 withdrew voluntarily

28 Patients Completed Study

14 Patients Randomized to receive placebo
- 14 Patients Received Placebo
  - 0 lost to follow-up
  - 2 had Protocol violation
  - 0 decreased drug
  - 0 withdrew voluntarily

14 Patients Completed Study

42 Patients Completed the 1 Year Study

Liver Volume Decreases in OctLAR Patients

Individual patients (% change compared to baseline)

Liver volume (average % change compared to baseline)

Placebo  OctLAR

Kidney Volume Decreases in OctLAR Patients

Individual patients (% change compared to baseline)

Kidney volume (average % change compared to baseline)

- Placebo
- OctLAR

Patient Reported Outcomes

• SF-36v2 physical component summary (PCS) score (p<0.05)

• Significantly improved in response to OctreotideLAR (p<0.05):
  --- physical ability
  --- bodily pain

GFR Decreased in Both Treatment Groups

Placebo

OctreotideLAR

△ changes (ml)

p=0.67

Adverse Events

• Serious: 3 hospitalizations unrelated to drug

• Transient pain on injection site (1-3 days post-injection)

• Granuloma on injection site

• Transient mild diarrhea (1-3 days post-injection)

• Other side effects:
  - gas
  - abdominal pain
  - headache

Summary

- 12 months of OctLAR treatment reduced liver and kidney volumes
- General health perception of PLD patients was improved on OctLAR
- Side effects of OctLAR were acceptable

Sirolimus (Rapamycin, Rapamune®)

- Discovered >30 years ago
- Anti-cancer activity known since mid-1970s.
- Natural compound made by *Streptomyces hygroscopicus*.
- Binds FK506 binding protein (FKBP-12) in a molecular complex that involves the subunit regulatory associated protein of TOR (RAPTOR), and inhibits mTOR kinase activity.
- Inhibition of mTOR: downregulation of CDK complexes and p27 (Kip1) accumulation; blocks cell-cycle progression in late G1/S.
- Inhibits proliferation of endothelial & vascular smooth muscle cells required for tumor angiogenesis.
Effects of Rapamycin on development of PKD in Han:SPRD rats.
TLV In Each Individual Patient At The First & Second Imaging Studies

**A**

+ Sirolimus

- Male
- Female

**B**

- Sirolimus

Total liver volume (L)

Before | After
---|---

Qian, Q. et al. JASN 2008;19:631-638
Average Changes in TLV in ADPKD Patients

Sirolimus

mTOR Inhibitors:

Sirolimus reduced cystic area and liver weight in Pkd2 mouse


No effect of Sirolimus on liver disease in PCK rat.

Renken et al. ePub NDT 2010.

Table 3. Effect of sirolimus on progression of hepatic disease in PCK rats and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>PCK male</th>
<th>SD male</th>
<th>PCK female</th>
<th>SD female</th>
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<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Sirolimus</td>
<td>Vehicle</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>LW/TBW (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>5.43 ± 0.27*</td>
<td>5.41 ± 0.50*</td>
<td>4.19 ± 0.04</td>
<td>4.29 ± 0.29</td>
</tr>
<tr>
<td>8 weeks</td>
<td>5.21 ± 1.22*</td>
<td>3.34 ± 0.01*</td>
<td>2.90 ± 0.21*</td>
<td>2.70 ± 0.16*</td>
</tr>
<tr>
<td>12 weeks</td>
<td>4.42 ± 0.74*</td>
<td>4.77 ± 0.35*</td>
<td>2.48 ± 0.10*</td>
<td>2.50 ± 0.15*</td>
</tr>
<tr>
<td>Cyst area/liver area (%)</td>
<td>2.70 ± 0.77</td>
<td>3.47 ± 1.14</td>
<td>2.48 ± 0.10</td>
<td>2.50 ± 0.15</td>
</tr>
<tr>
<td>4 weeks</td>
<td>5.87 ± 2.99</td>
<td>8.23 ± 4.21</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>8 weeks</td>
<td>7.67 ± 8.55</td>
<td>4.56 ± 0.99</td>
<td>5.10 ± 2.00</td>
<td>4.82 ± 1.32</td>
</tr>
<tr>
<td>12 weeks</td>
<td>5.86 ± 5.89</td>
<td>2.70 ± 1.14</td>
<td>6.31 ± 1.40</td>
<td>6.57 ± 1.10</td>
</tr>
<tr>
<td>Fibrosis area/liver area (%)</td>
<td>8.06 ± 3.26</td>
<td>6.85 ± 2.82</td>
<td>8.06 ± 3.26</td>
<td>6.85 ± 2.82</td>
</tr>
<tr>
<td>4 weeks</td>
<td>12 weeks</td>
<td>8.26 ± 7.76</td>
<td>5.76 ± 2.91</td>
<td>5.58 ± 2.39</td>
</tr>
<tr>
<td>8 weeks</td>
<td>9.38 ± 4.52</td>
<td>7.53 ± 3.68</td>
<td>6.55 ± 2.66</td>
<td>6.63 ± 2.04</td>
</tr>
<tr>
<td>12 weeks</td>
<td>11.38 ± 6.09</td>
<td>8.35 ± 4.02</td>
<td>9.38 ± 4.52</td>
<td>7.53 ± 3.68</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>35.8 ± 8.84*</td>
<td>83 ± 3.18*</td>
<td>35.8 ± 8.84*</td>
<td>83 ± 3.18*</td>
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<tr>
<td>4 weeks</td>
<td>81.5 ± 55.7</td>
<td>121 ± 33.5</td>
<td>81.5 ± 55.7</td>
<td>121 ± 33.5</td>
</tr>
<tr>
<td>8 weeks</td>
<td>85.7 ± 20.0</td>
<td>164 ± 06.09</td>
<td>85.7 ± 20.0</td>
<td>164 ± 06.09</td>
</tr>
<tr>
<td>12 weeks</td>
<td>59.9 ± 9.93</td>
<td>65.3 ± 24.8</td>
<td>59.9 ± 9.93</td>
<td>65.3 ± 24.8</td>
</tr>
<tr>
<td>ASAT (U/L)</td>
<td>92.4 ± 96.0</td>
<td>68.2 ± 45.3</td>
<td>92.4 ± 96.0</td>
<td>68.2 ± 45.3</td>
</tr>
<tr>
<td>4 weeks</td>
<td>66.4 ± 20.8</td>
<td>62.5 ± 17.0</td>
<td>66.4 ± 20.8</td>
<td>62.5 ± 17.0</td>
</tr>
<tr>
<td>8 weeks</td>
<td>366 ± 94.99</td>
<td>506 ± 55.3</td>
<td>366 ± 94.99</td>
<td>506 ± 55.3</td>
</tr>
<tr>
<td>12 weeks</td>
<td>382 ± 100</td>
<td>390 ± 125</td>
<td>382 ± 100</td>
<td>390 ± 125</td>
</tr>
</tbody>
</table>

Results are given as means ± SD.

*P < 0.05 (sirolimus-treated animals versus vehicle-treated PCK and SD rats, respectively).

Renken et al. ePub NDT 2010.
Symptomatic Polycystic Liver Disease
Nonsurgical Treatment Options

• Avoid estrogens, caffeine

• $H_2$-blocker or $H^+/K^+$ ATPase inhibitor

• Somatostatin analogues

• mTor inhibitors (?)
  
  • May have a future role but because of toxicity is not likely to have a major impact as single drug.
Acknowledgments:

- Vicente Torres MD PhD
- Peter Harris PhD
- Chris Ward MD PhD
- Tatyana & Anatoly Masyuk, Nick LaRusso MD.
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- page.linda@mayo.edu
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  - Mayo Foundation.
  - Novartis.
Liver Disease in ADPKD

WEBINAR, July 13th 2010.

Marie Hogan MD PhD
Assistant Professor, Division of Nephrology & Hypertension,
Mayo Clinic, Rochester, MN.
Drug Dosing

Tubular Cell proliferation in Cysts Markedly Reduced.

PCNA-positive cells in tubular epithelial cells lining the cysts was significantly decreased by rapamycin. *$P < 0.05$ versus vehicle-treated Cy/+ rats.

PCNA staining (arrows) in cysts of vehicle-treated Cy/+ rats.

PCNA staining (arrows) in cysts of rapamycin-treated Cy/+ rats.

Tao, Y. et al. JASN. 2005;16:46-51