Traitement de la PKRD: Analogues De La Somatostatine

Treatment of ADPKD : Somatostatin Analogues

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Disclosures:

• Roche:
  • Consulting

• Novartis:
  • Grant support for clinical study
  • Octreotide LAR

• Otsuka:
  • Site Sub-investigator
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

1:400-1,000 (5% sporadic)

Fourth cause of ESRD

\( PKD1 > PKD2 \)

ESRD 54 (\( PKD1 \))-74 (\( PKD2 \)) yrs

Systemic Disorder
• Total 1003 variants
  – PKD1 = 864 (86.1%); PKD2 = 139 (13.9%)
• 551 Likely Pathogenic mutations
  – PKD1 = 436 (544 families); PKD2 = 115 (198 families)
• 71 Indeterminate change
  – PKD1 = 67 (94.4%); PKD2 = 4 (5.6%)
• 377 Neutral polymorphisms
  – PKD1 = 357 (94.7%); PKD2 = 20 (5.3%)
ADPKD Mutation Distribution:

No mutation identified in 8.9% families

Non-definite mutation identified in 27.2% families

Definite (truncating) mutation identified 63.9%

- No mutation identified in 8.9%
- Non-definite mutation identified in 27.2% families
- Definite (truncating) mutation identified 63.9%

Rossetti 2007 JASN; Consugar 2008 KI
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
## Polycystic Liver Disease:

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<tr>
<th>Disease</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Protein</th>
<th>Function</th>
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<td>PKD1</td>
<td>16p13.3</td>
<td>Polycystin 1</td>
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<td>6</td>
<td>SEC63</td>
<td>ER protein processing</td>
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</table>
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 (37.6ml).
- 30yo woman hepatic cysts (2368.8 ml) and renal cysts (1084.5 ml).

Bae, K. T. et al. CJASN 2006;1:64-69
Autosomal Dominant Polycystic Liver Disease:

- Less common
- Prevalence at autopsy of 0.05%-0.53%
- Mutations in \textit{PRKCSH} or \textit{Sec63}
- Few or no kidney cysts
- Renal function is normal
- \~40\% with mutations in known genes
Cystogenesis in ADPKD/ADPLD:
Symptoms in Polycystic Liver Disease:

- Abdominal distension/pain
- Early satiety, GE reflux, 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 (2):

Acute Complications
- Hemorrhage
- Rupture
- Infection

Rare Associations
- Bile duct dilatation
- Congenital hepatic fibrosis
- Cholangiocarcinoma
PLD: One Treatment Does Not Fit All:

Sclerosis or Fenestration

Resection/Fenestration

Liver Transplantation
Liver Transplantation for Massive Polycystic Liver Disease.
51yo (59kg) With ADPKD With A 9.1-kg Liver Underwent Liver Transplant

Wall WJ. NEJM 2007.
Mechanisms of Cyst Development:

Mutations in ADPKD and ADPLD genes

- Defective cell planar polarity
- Centrosomal amplification
- Increased apoptosis

Secretory Phenotype
- Increased cell proliferation

\[ \text{cAMP elevation} \]
In Cholangiocytes, cAMP Facilitates Fluid Secretion & Proliferation:

Two major processes involved in cyst expansion

Basolateral (blood)

Apical (bile)

Meal → Secretin → [↑cAMP]

↑ MAPK

↑ MMAPK

↑ mTOR

Fluid secretion

Cl⁻, HCO₃⁻, H₂O

**SSTRs, Somatostatin and Octreotide:**

- Somatostatin receptors (SSTR): 1, 2, 3, 4, 5
- G-coupled receptors that bind somatostatin
- Somatostatin present in pancreas, kidneys

![Diagram of Somatostatin](image)

(peptide inactivation)

*Half-life time - 2-3 min*

- Octreotide (SMS-201-995), stable analog of somatostatin

![Diagram of Octreotide](image)

*Octreotide is 45-70 times more potent*

- Octreotide binds to SSTRs 2, 5 and 3
In Cholangiocytes, cAMP Facilitates Fluid Secretion And Proliferation

SSTR2: Cell proliferation
SSTR3: Apoptosis

Basolateral (blood)

Apical (bile)

Fluid secretion

SSTR5

Normal

PCK

Somatostatin

Meal → Secretin

[cAMP]

Cl⁻

HCO₃⁻

H₂O

GH

IGF1

IL6,8

VEGF

mTOR

Proliferation
cAMP and Cholangiocyte Biology

- Secretin receptor: $\uparrow$[cAMP]
- Somatostatin Receptors (SSTRs): $\downarrow$[cAMP]
In Cholangiocytes, SST Analogs Block Fluid Secretion:

**Basolateral** (blood)

- Somatostatin

**Apical** (bile)

- Secretin

MAPK
EGFR

\[ \downarrow \text{cAMP} \]

Fluid secretion

\[ \uparrow \text{cAMP} \] \[ \downarrow \text{cAMP} \]

\[ \text{Cl}^- \]
\[ \text{HCO}_3^- \]
\[ \text{H}_2\text{O} \]

**Proliferation**

Transport Mechanisms Involved In cAMP-dependent Cl⁻ Secretion By ADPKD Cyst Epithelial Cells In The Kidney:
↑RPF, ↑GFR, ↑urine volume, ↓C_{osm} & ↓C_{H2O}

Secretin

↓GFR, ↓RPF, ↓urine volume, ↓C_{osm} & ↓C_{H2O}

Podocytes 1*, 2*
Mesangial & Tubular cells secrete

Proximal tubule

2* Principal cells

Collecting duct

Arcuate vein

Ascending Vasa Recta (AVR)

Loop of Henle

Descending Vasa Recta (DVR)

Giomerulus

Arcuate artery

Mouse *
Rat ○
Human ■

SRIF = Somatostatin

cAMP cell proliferation

1*, 2*

3*, 4*, 5*

SRIF
The Secretin Receptor is Expressed Throughout the Kidney:

Secretin receptor:

Secretin may enhance H$_2$O absorption

Somatostatin May Blunt Cyst Development By Acting At Multiple Levels:

- Inhibition of secretin secretion by pancreas

![Diagram showing the effects of somatostatin on cyst development]

- Meal → Secretin
- 
- [↓cAMP]
- 
- Apical (bile)
- Fluid secretion
- GH
- IGF1
- IL6,8
- VEGF
- mTOR
- Proliferation
cAMP is Elevated in Cholangiocytes the PCK Rat, an Animal Model of PLD

Octreotide Inhibits Hepatic Cystogenesis in a Rodent Model of PLD by Reducing Cholangiocyte cAMP.

- Effect of Octreotide treatment on cAMP levels, liver weight, hepatic cyst volume, and hepatic fibrosis in vivo in PCK rats.

- This preclinical study provided a strong rationale for assessing the potential value of Octreotide in the treatment of PLD.

(A) Time-dependent & (B) dose-dependent (B) effect of octreotide treatment. (C) Liver sections from PCK rats treated with saline or octreotide. *P < .05.

Suppression of Elevated cAMP Levels in the PCK Rat by Octreotide Inhibits Hepatic and Renal Cystogenesis

Representative Images of Abdominal CT Scans of an ADPKD Patient for a Pituitary Adenoma.

- Before (A) Octreotide

- 2 years’ treatment (B) with Octreotide
  - No increase in cyst areas
  - No change in creatinine
**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).**

\[ \Delta \text{TLV} (-66 \text{ 56 vs } +5 \text{ 88 ml}). \]

Ruggenenti, Kidney Int, 68:206, 2005

Carolli. CJASN. 2010.
Normal Renal function.

Hepatomegaly & ascites, PLD & ruptured cyst.

Spironolactone 25–50 mg/d & furosemide 40 mg/day but ascites progressed.

Drainage of ascites (7 liters, serum ascites albumin gradient of 23.8 g/l) only temporary relief.

Octreotide (50 µg/h iv) was started 9 mo after the onset of ascites.

100 µg s/c (tid).

Three months-> pain free.

CT scan @ 112 days liver volume from 4609 ml to 2843 ml (38.3%)

Kidneys (left, 246 ml to 240 ml (2.4%); right, 554 ml to 455 ml (17.9%)).
Lockcyst Lanreotide Trial
Randomized, double blind, 1:1 placebo-controlled (6 months)

Absolute Volume Changes (ml): Liver
n=54

Volume Changes (%)

Liver
- Placebo: + 1.6 %
- Lanreotide: - 2.9 %
P-value <0.01

Kidney
- Placebo: + 3.4 %
- Lanreotide: - 1.5 %
P-value <0.02

van Keimpema. Gastroenterology 2009
Prospective, double blind, placebo controlled (2:1), 42 patients

Octreotide LAR ® 40 mg IM every 4 weeks
(two intragluteal 20 mg injections).

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

Secondary endpoints:
(1) Effect of Octreotide LAR® Depot on the total kidney volume and iothalamate clearance in patients with PKD associated with severe PLD
(2) Evaluate quality of life changes (QOL SF-36v2TM)
(3) Assess toxicity of Octreotide LAR® Depot.
113 Patients 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 Deviation
  - 7 Decreased to 30mg
  - 4 Decreased to 20mg
  - 3 Dose(s) withheld
  - 0 Withdrawed voluntarily

14 Patients Randomized to Receive Placebo

- 14 Patients Received Placebo
  - 0 Lost to follow-up
  - 2 Had Protocol Deviation
  - 0 Decreased Drug
  - 0 Withdrawed Voluntarily

28 Patients Completed Yr 1 Study

14 Patients Completed Yr 1 Study

41 Patients Received OctLAR

- 33 tolerated 40mg
- 5 Decreased to 30 mg
- 1 Decreased 20mg mo13 -24
- 1 Dose reduction (20 mg) due to diarrhea, then increased (30mg → 40mg) on resolution
- 1 Increased 30 mg→ 40mg due to resolution of diarrhea
- 1 Missed a dose
- 1 Withdrawed voluntarily

Year 2: Open Label OctLAR

- 41 Patients Completed the 2nd Year of Study
Mean (± SD) total Liver volumes at baseline, yr 1 & yr 2 (measured by MRI)

Patients originally on placebo decreased TLV on OctLAR in Yr 2 (Δ% -7.66 9.69%; p = 0.011).

Reduction in TLV in OctLAR group maintained, but did not increase significantly Yr2 (Δ% -5.96 8.90%; p =0.002).
Abdominal & Pelvic MRIs Demonstrating Reduction In Liver Cyst Burden With Two Years Of OctLAR Therapy.

Patient 1 had decrease of 25%

Patient 2, 10%

Patient 3, a 13% decrease in total liver volume.
OctLAR Inhibited Kidney Growth In Year 1, But Not Significantly During Year 2.
## Laboratory Parameters At Start & End Of Each Treatment Period.

<table>
<thead>
<tr>
<th></th>
<th>Octreotide</th>
<th>Placebo</th>
<th>P value (two sample t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient number</td>
<td>28 (Baseline)</td>
<td>26 (24 mo)</td>
<td>14 (Baseline)</td>
</tr>
<tr>
<td>Creatinine (mg/dL) (w/o ADPLD)</td>
<td>1.1 (0.43)</td>
<td>1.2 (0.62)</td>
<td>1.1 (0.52)</td>
</tr>
<tr>
<td>Patients (w/o ADPLD)</td>
<td>24</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>Creatinine w/o ADPLD</td>
<td>1.0 (0.44)</td>
<td>1.3 (0.65)</td>
<td>1.2 (0.56)</td>
</tr>
<tr>
<td>Patient number (w/o ADPLD)</td>
<td>21</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>iohalamate GFR (mL/min/1.732)</td>
<td>68.1 (26.53)</td>
<td>57.7 (23.52)</td>
<td>70.8 (28.08)</td>
</tr>
<tr>
<td>Prothrombin time (PT INR)</td>
<td>9.8 (0.71)</td>
<td>10.6 (0.62)</td>
<td>10.9 (5.22)</td>
</tr>
<tr>
<td>Patient number</td>
<td>28</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>AST</td>
<td>32.5</td>
<td>27.1</td>
<td>28.6</td>
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<td>Albumin</td>
<td>4.3</td>
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<td>Alkaline phosphatase</td>
<td>92.5</td>
<td>94.3</td>
<td>107.5</td>
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<td>26</td>
<td>13</td>
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<tr>
<td>Bilirubin</td>
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<td>0.6</td>
<td>1.0</td>
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<td>14</td>
</tr>
<tr>
<td>Blood glucose mg/dL</td>
<td>93.4 (11.22)</td>
<td>100.5 (15.01)</td>
<td>93.6 (7.81)</td>
</tr>
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<td>20</td>
<td>8</td>
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<tr>
<td>BUN (w/o ADPLD)</td>
<td>19.5 (7.23)</td>
<td>21.4 (9.68)</td>
<td>18.5 (7.39)</td>
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</tbody>
</table>
Patient Reported Outcomes at 2 Years:

• **SF-36 physical component summary (PCS) score (p<0.05)**
  • All 8 subdomains showed continued improvement over the 24 months of Oct LAR treatment

• **Significantly improved in response to OctLAR (p<0.05):**
  • Vitality
  • Physical ability
  • Bodily pain

Hogan et al. ASN 2010.
# ADPKD: CLINICAL TRIALS

<table>
<thead>
<tr>
<th><strong>Completed</strong></th>
<th><strong>Currently active</strong></th>
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<tr>
<td>TEMPO 250*</td>
<td>TEMPO 251</td>
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<tr>
<td>Tolvaptan Japan</td>
<td>ALADIN <em>(Bergamo)</em> (end Dec 2011)</td>
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<tr>
<td>Bergamo Octreotide</td>
<td>LOCKCYST <em>lanreotide autogel</em> 90 mg &amp; 120 mg; n=62; 6/2011-2/2013</td>
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<tr>
<td>Nijmegen-Leuven Lanreotide*</td>
<td>ELATE <em>(Octreotide LAR &amp; Everolimus 2.5mg)</em> n=44; 6/10-6/2012</td>
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<tr>
<td>Mayo Octreotide*</td>
<td><strong>Cleveland Clinic</strong></td>
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<tr>
<td>Everolimus <em>(Freiburg)</em></td>
<td><strong>Yale University</strong></td>
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<tr>
<td>SIRENA <em>(Bergamo)</em></td>
<td><strong>Mayo PLD after Renal TX</strong></td>
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<tr>
<td><strong>SUISSE</strong> <em>(Zurich)</em></td>
<td><strong>Triptolide</strong> <em>(Nanjing)</em></td>
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</table>

* extensions currently active

V2R antagonist
SST analog
mTOR inhibitor
ACEI, ARB, BP Statin

Pravastatin *(Colorado)*
SUMMARY: Opportunities and Challenges

- Somatostatin analogs are potential therapies for PKD & PLD
  - Sustains shrinkage in liver volume over two years
  - Kidney volumes decreased Year 1 & in year 2 P->O
  - Improved QOL over 2 years treatment
- Encouraging preliminary results with somatostatin analogs
- Relatively non-toxic
- Long-term safety and sustained efficacy need to be proven
- Possible role in future as combination therapies
• THE END
<table>
<thead>
<tr>
<th>Treatment Yr 0.1 / Yr 1.2</th>
<th>Mean (SD)</th>
<th>Paired t-test P value</th>
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<td>Baseline</td>
<td>Year 1</td>
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<tr>
<td><strong>Octreotide / Octreotide</strong></td>
<td>1152 (869)</td>
<td>1139 (838)</td>
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<td>Kidney total (N=19)</td>
<td>5984 (2961)</td>
<td>5628 (2720)</td>
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<td>Liver (N=26)</td>
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<tr>
<td><strong>Placebo / Octreotide</strong></td>
<td>803 (269)</td>
<td>874 (306)</td>
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<td>Kidney total (N=8)</td>
<td>5099 (3070)</td>
<td>5360 (3331)</td>
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<td>Liver (N=14)</td>
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Effects Of Somatostatin Analogues In Kidney:

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<th>SST₁</th>
<th>SST₂ₐ</th>
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From bench to bedside
↑RPF, ↑GFR, ↑urine volume, ↓C_{osm} & ↓C_{H2O}

**Secretin**

↓GFR, ↓RPF, ↓urine volume, ↓C_{osm} & ↓C_{H2O}

Podocytes 1*, 2*

Mesangial & Tubular cells secrete

**SRIF**

Proximal tubule

2* Principal cells

Collecting duct

Arcuate vein

Ascending Vasa Recta (AVR)

Mouse *

Rat ○

Human ■

SRIF = Somatostatin
Polycystic Kidney Disease, From Bench to Bedside
June 26- July 1
Saxtons River, Vermont

Co-Organizers:
Peter C. Harris
Mayo Clinic
Rochester, MN

Dorien Peters
Leiden University Medical Center
Leiden, The Netherlands

Jim Calvet
University of Kansas Medical Center
Kansas City, KS
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/m^2)</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.

Resection-Fenestration for Polycystic Liver Disease

Distribution of Segmental Resection

![Diagram of liver segments and bar chart showing distribution of segmental resection.](image-url)
<table>
<thead>
<tr>
<th>Treatment Yr 0.1 / Yr 1.2</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>% Δ 0.1</th>
<th>% Δ 1.2</th>
<th>% Δ 0.2</th>
<th>% Δ 1.2 - % Δ 0.1</th>
</tr>
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<tr>
<td><strong>Octreotide / Octreotide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney total (N=19)</td>
<td>1152 (869)</td>
<td>1139 (838)</td>
<td>1214 (884)</td>
<td>0.42 (7.61)</td>
<td>6.49 (7.08)</td>
<td>7.01 (11.49)</td>
<td>0.81</td>
</tr>
<tr>
<td>Liver (N=26)</td>
<td>5984 (2961)</td>
<td>5628 (2720)</td>
<td>5649 (2870)</td>
<td>-5.23 (6.22)</td>
<td>-0.77 (6.82)</td>
<td>-5.96 (8.90)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Placebo / Octreotide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney total (N=8)</td>
<td>803 (269)</td>
<td>874 (306)</td>
<td>885 (355)</td>
<td>8.61 (10.07)</td>
<td>0.41 (9.45)</td>
<td>NA</td>
<td>0.0462</td>
</tr>
<tr>
<td>Liver (N=14)</td>
<td>5099 (3070)</td>
<td>5360 (3331)</td>
<td>4952 (3344)</td>
<td>3.69 (10.53)</td>
<td>-7.66 (9.69)</td>
<td>NA</td>
<td>0.21</td>
</tr>
</tbody>
</table>
From bench to bedside

**Reduced in PKD**
- KCa3.1 inh
- CFTR inh
- TNF antagonist
- PC2 inh

**Increased in PKD**
- PC1 inh
- Triptolide
- Thiophene-carboxylate

**Protein synthesis**
- mTOR
- GSK3β
- CDK inhibitors
- Somatostatin
- sFRP4 inhibitors

**Nucleus**
- Myc
- Jun
- Phos
- CyclinD

**Proteasome**
- β-Catenin

**Ca2+**
- ER
- SOC
- PC2

**AMPK**
- Metformin
- LKB1

**Na+ K+ ATPase**
- Na+ K+ ATPase
- Na+ K+ Cl- ATPase

**GSK3β**
- Dvl

**Src inh**
- MEK inh
- MEK
- Ras
- B-Raf

**PKA**
- PKA
- PKA

**AMP**
- cAMP
- PDE

**ATP**
- ATP

**Gi**
- V2R
- Gi
- AC-VI

**Gs**
- V2RA
- Gs

**PLCγ**
- R
- R

**Na+ K+ ATPase**
- Na+ K+ ATPase

**From bench to bedside**
Kidney vol increased by $71 \pm 107 \text{ mL} \ (P < 0.05)$ on treatment and by $162 \pm 114 \text{ mL} \ (P < 0.01)$ on placebo.

Somatostatin: volume incr $\sim 60\% <$ placebo.

Total volume increase during placebo treatment was renal cysts ($106 \pm 105 \text{ mL} \ (P < 0.01)$; only marginally influenced by concomitant changes in the "parenchymal" volume, which increased by only $9 \pm 22 \text{ mL}$.

Increase in kidney volume during treatment with somatostatin was entirely due to increase in cysts ($61 \pm 106 \text{ mL}$), since the "parenchymal" volume actually numerically decreased by $10 \pm 24 \text{ mL}$.
Patients Included In Placebo Or Octreotide Group Have Similar Clinical Data

<table>
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<tr>
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<th>Octreotide (%)</th>
<th>Placebo (%)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>n=28</td>
<td>1 (7.1%)</td>
<td>0.64*</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>13 (92.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td>49.7</td>
<td>50.3</td>
<td></td>
</tr>
<tr>
<td><strong>Median Age (range)</strong></td>
<td>47.4 (34.8-69.3)</td>
<td>50.3 (38.8-65.7)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Weight (SD)</strong></td>
<td>76 (20.2)</td>
<td>70.9 (10.89)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Weight range</strong></td>
<td>50.3-129.5</td>
<td>55.6-92.8</td>
<td></td>
</tr>
<tr>
<td><strong>Median BMI</strong></td>
<td>24.6</td>
<td>24.2</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Median Creatinine</strong></td>
<td>0.9</td>
<td>0.8</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>GFR (range)</strong></td>
<td>70 (20-124)</td>
<td>71 (22-115)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Glucose (fasting)</strong></td>
<td>93</td>
<td>94</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Albuminuria (mg/24 hour)</strong></td>
<td>65 (124)</td>
<td>130 (238)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Total kidney volume (n)</strong></td>
<td>28 688 (246-3351)</td>
<td>12 585 (300-1210)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Liver volume</strong></td>
<td>28 4973 (2018-11591)</td>
<td>14 4229 (2109-12489)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Data are mean ± SD and median- and (range) P values; rank sum test. * = Fisher's exact test. GFR measured by iothalamate clearance in all patients with renal cysts.
The Belgium trial will be with Lanreotide:

Lanreotide Autogel is a new long-acting aqueous preparation of lanreotide for the treatment of acromegaly and is administered by deep sc injection from a small volume, prefilled syringe. The aim of this study was to evaluate the efficacy and safety of this new long-acting formulation in a large population of acromegalic patients previously responsive to lanreotide 30 mg, im (sustained release microparticle formulation). Lanreotide Autogel was administered by deep sc injection every 28 d to 107 patients (54 males and 53 females; mean age, 54 ± 1.2 yr). All patients had been treated with lanreotide (30 mg) for at least 3 months before study entry and had a mean GH level less than 10 ng/ml after at least 4 subsequent im injections every 14 d (48%), 10 d (32%), or 7 d (20%). Treatment was switched from lanreotide 30 mg injected every 14, 10, or 7 d to 60, 90, or 120 mg lanreotide Autogel, respectively, every 28 d. After three fixed dose injections of lanreotide Autogel, mean lanreotide levels were similar to those obtained at steady state with lanreotide 30 mg. During lanreotide Autogel treatment, the control of acromegalic symptoms was comparable with that previously achieved during lanreotide 30 mg treatment. After 3 injections of lanreotide Autogel, mean GH (2.87 ± 0.22 ng/ml) and IGF-I (317 ± 15 ng/ml) values were comparable with those recorded at the end of lanreotide 30 mg treatment (GH, 2.82 ± 0.19 ng/ml; IGF-I, 323 ± 16 ng/ml). GH levels below 2.5 ng/ml and age-/sex-normalized IGF-I were achieved in 33% and 39% of patients during lanreotide 30 mg and lanreotide Autogel treatment, respectively. Diarrhea, abdominal pain, and nausea were reported by 38%, 22%, and 18% of patients during lanreotide 30 mg treatment and by 29%, 17%, and 9% of patients, respectively, during lanreotide Autogel treatment. In conclusion, this clinical study shows that lanreotide Autogel is at least as efficacious and well tolerated as lanreotide 30 mg. This new long-acting lanreotide formulation, lanreotide Autogel, which is administered from a small volume, prefilled syringe by deep sc injection, is therefore likely to improve the acceptability of medical treatment for patients requiring long-term somatostatin analog therapy.
Average Changes In Kidney Volume, Cyst Volume, And "Parenchymal" Volume, And In The Whole Study Group At The End Of Placebo And Somatostatin Treatment.

- Numerically lower growth of cyst volume on somatostatin than on placebo (3.0 ± 6.5% vs. 5.6 ± 5.8%) and of opposite changes in "parenchymal volume," that non significantly decreased by 4.4 ± 8.9% on somatostatin, but actually increased by 2.5 ± 8.4%, on placebo
- Student t test for paired data.
Safety

- One patient developed cholelithiasis
  - Treatment withheld x few mo
  - disappeared after a few months of treatment with ursodeoxycholate acid.

- Three patients -watery diarrhea
  - spontaneously recovered during the first month of somatostatin therapy;
  - occasionally reported as a side effect of octreotide treatment.

- No deleterious changes in laboratory parameters were observed during somatostatin therapy.
Kidney, And Cystic Volumes Before & After Treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>Somatostatin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Serum creatinine mg/dL</td>
<td>2.0 ± 1.0</td>
<td>2.2 ± 1.1</td>
<td>1.9 ± 0.8</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>Diuresis mL/24 hours</td>
<td>1954 ± 599</td>
<td>2054 ± 590</td>
<td>1979 ± 530</td>
<td>2046 ± 667</td>
</tr>
<tr>
<td>Glomerular filtration rate mL/min/1.73 m²</td>
<td>57.9 ± 22.4</td>
<td>57.7 ± 25.7</td>
<td>59.5 ± 25.2</td>
<td>54.0 ± 23.6</td>
</tr>
<tr>
<td>Urinary albumin excretion μg/min</td>
<td>33 (9-543)</td>
<td>49 (8-595)</td>
<td>31 (13-437)</td>
<td>42 (7-543)</td>
</tr>
<tr>
<td>Resistive index, left</td>
<td>0.61 ± 0.07</td>
<td>0.64 ± 0.08</td>
<td>0.61 ± 0.08</td>
<td>0.64 ± 0.05</td>
</tr>
<tr>
<td>Resistive index, right</td>
<td>0.64 ± 0.06</td>
<td>0.65 ± 0.06</td>
<td>0.63 ± 0.07</td>
<td>0.66 ± 0.07</td>
</tr>
<tr>
<td>Total kidney volume mL</td>
<td>2461 ± 959</td>
<td>2623 ± 1021&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2551 ± 1053</td>
<td>2622 ± 1111&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyst volume mL</td>
<td>1656 ± 826</td>
<td>1762 ± 882</td>
<td>1709 ± 908</td>
<td>1770 ± 941</td>
</tr>
<tr>
<td>Parenchymal volume mL</td>
<td>242 ± 62</td>
<td>251 ± 72</td>
<td>247 ± 67</td>
<td>237 ± 65</td>
</tr>
<tr>
<td>Residual volume mL</td>
<td>562 ± 280</td>
<td>609 ± 325</td>
<td>595 ± 323</td>
<td>615 ± 347</td>
</tr>
</tbody>
</table>

Data are mean ± SD or median and (range). Student t test for paired data.

<sup>a</sup> $P < 0.05$;

<sup>b</sup> $P < 0.01$ vs. start.
Patient # 2: 43yo woman with PLD.

- Developed ascites & edema due to IVC syndrome, POD#11 days lap fenestration of liver cysts.
- Her weight had increased from 79 ->94 kg.
- In order to relieve the caval pressure, three cysts were aspirated and 14.5L of ascites was drained, without much benefit.
- One month after surgery, we started her on octreotide (100 µg tid s/c) and 12 days later switched to lanreotide (120 mg/mo s/c).
- 3D-volumetry of polycystic liver 230 days after start of treatment: volume decrease of 14.9% (8232->7004 ml).
- Renal function unchanged (creatinine 42 µmol/l-> 46 µmol/l).
Symptomatic Polycystic Liver Disease(2)

Complications

- Hemorrhage
- Rupture
- Infection

Rare Associations

- Bile duct dilatation
- Congenital hepatic fibrosis
- Cholangiocarcinoma
Randomized, Longitudinal, Cross-over Study: Safety & Efficacy Of Somatostatin For 6 Months

- Spiral CT
- Two monthly labs
- N=14
Kidney Segmentation In Two Different Patients With Cyst Different Morphology Of Cyst And Parenchymal Volumes.

Original images (A and C) are compared with corresponding pixel identification (B and D).

In segmented images white pixels represent parenchymal volume, dark gray pixels represent cyst area, while light gray pixels represent transitional area between parenchyma and cyst volume.

The number of pixels of the parenchyma and cysts areas used to calculate total volume, taking into account pixel dimensions and the distance between two slices.

Phantom validation: mean error< 0.7%
Administration of OctreotideLAR to a patient with severe PCLD results in decreased liver and kidney volumes.

Liver - 18%
Kidney - 12%

(Courtesy of Dr. Torres)
### ADPKD: CLINICAL TRIALS

#### Completed
- **TEMPO 250***
  - Tolvaptan Japan
- Bergamo Octreotide
- Nijmegen-Leuven Lanreotide***
- Mayo Octreotide***
- Everolimus (Freiburg)
- SIRENA (Bergamo)

*extensions currently active*

#### Currently active
- **TEMPO 251**
  - ALADIN (Bergamo)
  - SUISSE (Zurich)
  - Cleveland Clinic
  - Yale University
  - Mayo PLD after Renal TX
  - Triptolide (Nanjing)
  - HALT PKD
  - Pravastatin (Colorado)

**V2R antagonist**  
**SST analog**  
**mTOR inhibitor**  
**ACEI, ARB, BP**  
**Statin**
In Cholangiocytes, cAMP Facilitates Fluid Secretion And Proliferation:

Meal → Secretin

Basolateral (blood)

Apical (bile)

Fluid secretion

[cAMP]↑

↑MAPK

↑MMAPK

↑mTOR

Cl⁻ → HCO₃⁻ → H₂O

Two major processes involved in cyst expansion

In Cholangiocytes, SST Analogs Block Fluid Secretion:

**Basolateral**
(blood)

Somatostatin

**Apical**
(bile)

Meal → Secretin

In Cholangiocytes, SST Analogs Block Fluid Secretion:

Basolateral (blood)

Apical (bile)

Two major processes involved in cyst expansion

Meal → Secretin

[cAMP]

↑ MAPK

↑ MMAPK

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Cl⁻

HCO₃⁻

H₂O

Fluid secretion

Proliferation
Basolateral (blood)

Somatostatin

Meal → Secretin

Apical (bile)

Fluid secretion

MAPK

EGFR

[↓cAMP]

Cl⁻

HCO₃⁻

H₂O

Proliferation
Classification Of PLD And Suggested Surgical Treatment

Long-term outcome after surgical treatment for PLD

- 141 patients (1985-2006)
- 87% women
- Age 51 1 years
- 85% functionally impaired (ECOG 1-3).
- 65% significant IVC or HV compression

- 124 partial hepatectomy/fenestration
- 10 cyst fenestration alone
- 7 liver transplantation (primary tx)

- 58% operative morbidity
- 4% operative mortality

- 75% ECOG normalized or improved
- 73% Returned to work full-time
- Health survey scores similar to general population
Randomized, Longitudinal, Cross-over Study: Safety & Efficacy Of Somatostatin For 6 Months

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- Two monthly labs
- N=14
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¹  \( P < 0.05 \);

²  \( P < 0.01 \) vs. start.
Kidney vol increased by 71±107 mL ($P < 0.05$) on treatment and by 162 ±114 mL ($P < 0.01$) on placebo.

- Somatostatin: volume incr ~60% < placebo.
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• One patient developed cholelithiasis
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  • disappeared after a few months of treatment with ursodeoxycholate acid.

• Three patients -watery diarrhea
  • spontaneously recovered during the first month of somatostatin therapy;
  • occasionally reported as a side effect of octreotide treatment.

• No deleterious changes in laboratory parameters were observed during somatostatin therapy.
Somatostatin Analogues Decrease Cyst Volume in PLD. CT scan prior to (A) & after treatment (B).

- Normal Renal function.
- Hepatomegaly & ascites, PLD & ruptured cyst.
- Spironolactone 25–50 mg/d & furosemide 40 mg/day but ascites progressed.
- Drainage of ascites (7 liters, serum ascites albumin gradient of 23.8 g/l) only temporary relief.
- Octreotide (50 µg/h iv) was started 9 mo after the onset of ascites.
- 100 µg s/c (tid).
- Three months-> pain free.
- CT scan @ 112 days liver volume from 4609 ml to 2843 ml (38.3%)
- Kidneys (left, 246 ml to 240 ml (2.4%); right, 554 ml to 455 ml (17.9%)).
Patient # 2: 43yo woman with PLD.

- Developed ascites & edema due to IVC syndrome, POD#11 days lap fenestration of liver cysts.
- Her weight had increased from 79 ->94 kg.
- In order to relieve the caval pressure, three cysts were aspirated and 14.5L of ascites was drained, without much benefit.
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- Renal function unchanged (creatinine 42 µmol/l-> 46 µmol/l).
Long-Acting Octreotide Trial

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

Octreotide LAR ® 40 mg IM every 4 weeks
(two intragluteal 20 mg injections).

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

Secondary endpoints:
(1) Effect of Octreotide LAR® Depot on the total kidney volume and iothalamate clearance in patients with PKD associated with severe PLD
(2) Evaluate quality of life changes (QOL SF-36v2TM)
(3) Assess toxicity of Octreotide LAR® Depot.

Open label extension
MAYO OCTREOTIDE TRIAL
Randomized, double blind, 2:1 placebo-controlled

Baseline Volumes (ml)

Liver

Placebo
Octreotide

n=14
n=28

Kidneys

Placebo
Octreotide

n=14
n=28

MAYO CLINIC
In Cholangiocytes, cAMP Facilitates Fluid Secretion And Proliferation

Somatostatin

Basolateral (blood)

Apical (bile)

Cl⁻ → HCO₃⁻ → H₂O → Proliferation

Meal → Secretin

SSTR2, SSTR3, SSTR5

Normal, PCK
**Reduced in PKD**
- PC1
- PC2
- CAML
- PDE

**Increased in PKD**
- ErbB
- CFTR
- CAMP

**Pathways and Proteins**
- PKA
- PKR
- PLCγ
- PLC
- mTOR
- TSC2/TSC1
- Ras-B-Raf-MEK-ERK
- Rheb
- AC-VI
- Gi
- Gs
- V2R
- Octreotide
- Vasopressin

**Markers**
- Ca^2+ (Reduced in PKD)
- Ca^2+ (Increased in PKD)
- IP_3
- cAMP
- ATP

**Nucleus**
- Cyclin D

**Protein Translation**
- Protein translation process

**Other Elements**
- Gi
- Gs
- ER
- SOC
- CP1247144
Genotyping of ADPKD and ADPLD patients

42 patients

32 patients with mutations identified

25 patients with *PKD1* mutations

6 patients with *PKD2* mutations

6 patients with *PRKCSH* and 1 with *SEC63* mutation

6 patients with NO mutations identified

3 patients with ADPKD

3 patients with ADPLD
In Cholangiocytes, cAMP Facilitates Fluid Secretion And Proliferation:

Meal $\rightarrow$ Secretin

Somatostatin

Basolateral (blood)

Apical (bile)

Fluid secretion

Proliferation

**cAMP** Facilitates Fluid Secretion And Proliferation:

SSTR2  SSTR3  SSTR5

HCO\(_3^-\)

H\(_2\)O

Cl\(^-\)

SSTR2  SSTR3  SSTR5

Normal PCK
In Cholangiocytes, cAMP Facilitates Fluid Secretion And Proliferation

Meal → Secretin

Basolateral (blood)

Apical (bile)

Fluid secretion

Proliferation

[cAMP]

[↑cAMP] [↓cAMP]

HCO$_3^-$

H$_2$O

Cl$^-$

Somatostatin

SSTR2 SSTR3 SSTR5
In Cholangiocytes, SST Analogs Block Fluid Secretion:

- **Basolateral** (blood):
  - Meal → Secretin
  - Somatostatin
  - MAPK
  - EGFR

- **Apical** (bile):
  - [↓cAMP]
  - \[cAMP\]
  - \[\text{HCO}_3^-\]
  - \[\text{H}_2\text{O}\]
  - \[\text{Cl}^-\]

Study Design: 2:1 Crossover:

Test dose 100 μg

Year 1

Monthly injections im

Year 2

Open Label Extension

Year 4

Injection Study drug/ placebo

Mayo Clinic Visit

Data analysis

MRI /GFR

N=42