Management of polycystic liver disease and other liver complications

Joost PH Drenth

KDIGO Controversies Conference on Autosomal Dominant Polycystic Kidney Disease (ADPKD)
January 16-19, 2014
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KDIGO Questions

1. What are the indications for intervention in PLD? How to choose the most appropriate treatment?
2. What are the medical therapies in PLD?
3. What are the side effects of somatostatin analogues?
4. Should hepatic cystic disease impact on choice of immunosuppression?
5. What are the barriers to clinical trials for PLD?
6. How to diagnose and treat liver cyst infections?
7. How to evaluate and follow PLD: Need to develop a clinical score or a specific questionnaire?
8. What advice can be given to pre- and post-menopausal women with PLD regarding contraception and estrogen replacement therapies?
Q1
What are the indications for intervention in PLD?
How to choose the most appropriate treatment?
Invasive treatment options

• Aim:
  • Improvement of Quality of Life
  • Reduction of symptoms

• Means:
  • Reduction of liver volume

• Invasive treatment options:
  • Radiological
    • Aspiration and sclerotherapy
    • Transcatheter arterial embolization
  • Surgical
    • Cyst fenestration
    • Liver resection
    • Liver transplantation
## Interventions in PLD

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Effect</th>
<th>Side effects</th>
<th>P.O.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant Cysts</td>
<td>Aspiration sclerotherapy</td>
<td>Total regression in 22%</td>
<td>Cyst bleeding infection</td>
<td>OK</td>
</tr>
<tr>
<td>Superficial large cysts</td>
<td>Fenestration</td>
<td>Symptom relief 92%</td>
<td>Complications 23%</td>
<td>OK</td>
</tr>
<tr>
<td>Segmental PLD</td>
<td>Hepatic Resection</td>
<td>Symptom relief 86%</td>
<td>Complications 51%</td>
<td>Do not try, unless...</td>
</tr>
<tr>
<td>Massive PLD</td>
<td>Embolization of hepatic artery</td>
<td>TLV 4% ↓</td>
<td>3-year survival 70%</td>
<td>Only in Japan</td>
</tr>
<tr>
<td>Massive PLD</td>
<td>Liver transplantation</td>
<td>QoL 91% ↑</td>
<td>Morbidity 41%</td>
<td>Do if out of options</td>
</tr>
</tbody>
</table>

Treatment Algorithm

Polycystic liver

Symptoms

- Cyst > 5 cm and percutaneously reachable
  + Aspiration-sclerotherapy
  - Laparoscopic fenestration

- Numerous cysts > 4 cm and laparoscopically reachable
  + Laparoscopic fenestration

- Extremely impaired quality of life; untreatable complications of polycystic liver
  + Liver transplantation

- Conservative treatment

No treatment

[Fig] Keimpema, Br J Surg 2009
Q2
What are the medical therapies in PLD?
Individual responses in somatostatin trials

[Fig] Gevers et al, Gastroenterology. 2013
Starting dose somatostatin analogues

- **Lanreotide**
  - 120 & 90 mg every 4 weeks decrease liver volume after 6 months dose-dependently[1]
  - Less pronounced side-effect profile in LAN 90 mg[1]
  - No correlation with serum levels and treatment response[2]
  - Start with 120 mg /4 weeks

- **Octreotide**
  - No dose-finding studies
  - Start with 40 mg every 4 weeks

Starting dose in reduced renal function

- Limited pharmacokinetic data

- Reduced clearance of lanreotide in 12 patients on dialysis\(^1\)
  - Including 3 ADPKD patients
  - After 1 bolus of 7 µg/kg lanreotide

- Dose reduction in ↓ GFR?
  - 120 → 90 mg in eGFR < 30 ml/min in DIPAK trial\(^2\)

\(^1\) Barbanoj et al, Clin Pharmacol Ther .1999
\(^2\) Meijer et al, Am J Kidney Dis. 2013
Somatostatin analogues in PLD

- Lanreotide & Octreotide reduce liver volume in PLD
  - Effect
    - Majority (80%) responds
    - Dose dependency (Lanreotide)
    - Within 3-6 months
    - Largest effect < 6 months, beyond: maintenance
    - Stopping = recurrence
    - Females > Males
    - Young > Old
    - Adding everolimus: no use
    - Curtails kidney volume?
Q3

What are the side effects of somatostatin analogues?
Monitoring side-effects

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Somatostatin analogue n/N (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Placebo n/N (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea/Loose stools</td>
<td>34/67 (51)</td>
<td>7/52 (13)</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>23/67 (34)</td>
<td>1/52 (2)</td>
</tr>
<tr>
<td>Flatulence, bloating and gas</td>
<td>20/67 (30)</td>
<td>3/52 (6)</td>
</tr>
<tr>
<td>Persistent injection site swelling</td>
<td>17/67 (25)</td>
<td>1/52 (2)</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>10/67 (15)</td>
<td>0/52 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9/67 (13)</td>
<td>3/52 (6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4/67 (6)</td>
<td>1/52 (2)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Denominator is total of patients in treatment arm

- **Management**
  - Most symptoms disappear after repeated injections
  - Dose reduction
  - Pancreatic enzyme suppletion
Monitoring side-effects

- **Cholelithiasis** [1,2]
  - No patient developed (symptomatic) cholelithiasis in trials (6-24 months)
    - However, no ultrasound follow-up

- **Plasma glucose levels** [3]
  - Significantly increases after SA therapy (+0.4 mmol/L in 6-12 months)
  - No patient developed diabetes or required antidiabetic therapy in trials
  - Dose reduction in case of hyperglycemia

Q4

Should hepatic cystic disease impact on choice of immunosuppression?
mTOR inhibitors after kidney transplantation

- 16 ADPKD patients: renal transplantation
- RCT: immunosuppressive effects sirolimus (n=7) vs. tacrolimus (n=9)
- Length of treatment 9.4 months; Abdominal imaging studies (-11 to +7 months)

mTOR does not potentiate effect of somatostatins

- mTOR inhibitors combined with somatostatin analogues
- 44 severe PLD patients
- Treatment 1 year
  - Octreotide LAR
  - Octreotide LAR and everolimus
- Everolimus does not improve volume-reducing effect of octreotide

Chrispijn et al, J Hepatol. 2013
Q5
What are the barriers to clinical trials for PLD?
Barriers

- Somatostatin analogues
  - May be perceived as standard of care
  - Placebo no clinical equipoise
- Inclusion criteria
  - Liver volume
  - Symptoms
- Primary endpoint?
  - Symptoms: no validated questionnaire
  - Liver volume:
    - Time consuming (not automated)
    - CT scan (radiation exposure)
    - MRI (expensive)
Q6
How to diagnose and treat liver cyst infections?
Cyst infection: diagnosis

- No validated diagnostic criteria \([1,2]\)
  - mix of elements: pain + fever + CRP
  - gold standard?

- **CA 19.9** \([3]\)
  - increased in hepatic cyst infection (serum and cyst)
  - however: CA 19.9 raised in 40% of ADPKD patients

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[1] Salleé et al. cJASN 2009
[3] and [Fig ] Kanaan et al. AJKD 2010
Cyst infection: diagnosis

- Imaging?
  - CT and MRI: contrast use, poor sensitivity/specificity
  - most promising technique: $^{18}$F-FDG-PET CT $^{[1-4]}$
    - limitations: costs, availability
    - sensitivity: effect of antibiotic treatment on result?
    - specificity: cholangitis, neoplasm?

[Fig] Lantinga et al. MAGMA 2013
Cyst infection: management

- Antibiotic therapy?
  1. adequate hepatic cyst penetration
    - limited data: fluoroquinolones (ciprofloxacin) [1]
  2. efficacy against common pathogens
    - resistance?
  3. duration and follow-up
    - short- vs. longterm?
    - usefulness of CRP and/or $^{18}$F-FDG-PET CT? [2]

- Cyst drainage?
  - identification and accessibility of infected cyst?
  - risk of infection spread?

- Perceived increased risk of infection after RTX [3,4]

[2] Lantinga et al. unpublished
Q7

How to evaluate and follow PLD: Need to develop a clinical score or a specific questionnaire?
Follow up

• Follow up liver volume
  • Growth rate: 0.9-1.6% in ½ - 1 year

• Physical examination
  • Weight
  • Abdominal girth
  • Nutritional state (midarm circumference)
  • Signs of caval vein compression/portal hypertension

• Symptoms
  • Adjusted MELD score
  • Disease specific questionnaire (available spring 2014)
    • Captures PLD specific symptoms
    • Assesses improvement/decline in PLD specific symptoms
    • Outcome measure clinical trials
Q8

What advice can be given to pre- and post-menopausal women with PLD regarding contraception and estrogen replacement therapies?
Estrogens use

- Female sex, estrogens use and multiple pregnancies are risk factors polycystic liver growth

- 20 postmenopausal ADPKD pts [1]
  - Estrogens use vs. no treatment
  - Estrogen treatment associated increase in liver volume; no increase in kidney volume

- Discourage the use of exogenous estrogens in symptomatic PLD patients [2]

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What should patients be told about PLD? Is enough known about potential lifestyle modifications (good and bad) to affect this frightening PKD-related condition?
Polycystic liver disease

• Patient information
• Lifestyle modifications
• Risk of complications
Practical Integrated Patient Support
Somatostatin analogues in age-gender subgroups

[Fig] Gevers et al, Gastroenterology. 2013
Extension trials

- Largest effect early in treatment
- Prolonging results in maintenance
- During follow-up: recurrence of liver growth

How to manage recurrent infection?

Serum CRP and $^{18}$F-FDG PET/CT results following ciprofloxacin antibiotic therapy

[Fig] Lantinga et al. *unpublished*
Follow up: Severe PLD

Follow up liver volume
- Growth rate: 0.9-1.6% in ½ - 1 year [1]

Adjusted MELD-score [2]
- Massive polycystic liver (total cyst:parenchyma ratio > 1)
- Not a candidate/ failure other therapies
- Clinically significant manifestations of PLD
- Severe malnutrition
- Serum albumin <2.2 mg/dL
- Lean body mass: ↓ midarm circumference
  - ≤ 23.1 cm females, ≤ 23.8 cm males

eGFR >30: 15 points
eGFR <30: 20 points

Evaluation and follow-up

• Aim of SA therapy: reducing PLD-related symptoms by decreasing liver volume

• Follow-up liver volume
  • CT or MRI volumetry
  • Time-consuming (± 1 hour)
  • Need for faster methods

• Follow-up symptoms

• Stopping rules?
Aspiration sclerotherapy

- Indication: large symptomatic solitary or dominant hepatic cyst (> 5 cm)

- Minimal invasive

- Procedure: percutaneous drainage with instillation of sclerosing agent [1]
  - Ethanol, minocycline, tetracycline, etc
  - Comparable results, ethanol most commonly used

- 22% total regression; 19% partial regression [2]
- 21% recurrence [2]

Transcatheter arterial embolization

- Procedure: selective embolization of hepatic artery branches that supply major cysts

- Experimental [1,2]
  - Two relatively small uncontrolled trails
  - Reduction liver volume by 23-36%
  - Symptomatic improvement

- Research in a controlled setting is needed before recommending TAE over conventional treatment options [3]

Cyst fenestration

- Indication: multiple symptomatic large superficial located cysts
- Procedure: deroofing cyst [1]
- 92% symptomatic relief; 24% cyst recurrence [2]
- Complications: laparoscopic 23% vs laparotomy 40% [2]

Segmental hepatic resection

- Indication: Severe polycystic liver with at least one unaffected segment
- Procedure: resection of affected segments and fenestration of residual cysts
- 86% symptomatic relief[^1]
- Complications in 51%; mortality 3%[^1]
- Risk of subsequent adhesions might complicate future liver transplantation[^2]

Liver transplantation

- Indication: severe diffuse polycystic liver with grave impaired quality of life and/or untreatable complications [1]

- Curative treatment option; 91% improvement of quality of life [2]

- Morbidity: 41%

- Liver and kidney transplantation
  - Consider in ADPKD patients undergoing maintenance dialysis

- 5 year survival rate: 92% LTx and 80% LKTx [3]

[3] and [Fig] van Keimpema Transpl Int 2011; 24(12): 1239-1245
Follow up: Quality of life

Follow up: Laboratory findings

- No abnormalities in liver synthesis

- Abnormalities in liver enzymes may occur:
  - ↑ γGT \(^1\)
  - ↑ AP \(^1\)

- ↑ Bilirubin by compression of bile ducts \(^1\)

- ↑ Carbohydrate antigen 19-9 \(^2\)
  - Positive correlation with liver volume \(r = 0.3870, P = 0.0025\)
  - Raised in cyst infections \(^3\)
  - Possible follow up biomarker?

\(^1\) Van Keimpema L et al., Liver Int. 2011 Jan; 31(1):92-8