ADPKD Clinical Research Update

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Topics Covered

• Loss of Kidney Function in ADPKD
  – CRISP Trial Results

• Potential Therapies

• Slowing Progression of ADPKD:
  – Tolvaptan Clinical Trial
  – HALT PKD Clinical Trial
  – Somatostatin
  – Sirolimus (Rapamycin)

- The disease of polycystic kidneys in adults is homochronous, that is, the malformation first shows signs or symptoms after the age of 30-40, and progresses mercilessly with greater or lesser rapidity. The genetically determined disease process is latent for many years, and then becomes manifest in a kidney tissue which has apparently developed and functioned normally.

Early Stage of Cystogenesis

Baert, Kid. Int. 13:519, 1978
ADPKD is a slowly progressive kidney disease and, therefore, hard to study

- Filtration (GFR) stable for many years; rapid decline after 50% of function is lost
  - Males 5 - 6 ml/min/year; Females 4 - 5 ml/min/year
- 50% of patients require dialysis/transplant by age 60
- No impact on rate of decline of filtration with dietary protein restriction
- Effect on filtration decline of antihypertensive Rx with ACE-I uncertain
Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)  

**Study Completed**

- Observational trial (no intervention) to determine how to assess changes in polycystic kidneys over a relatively short period of time (3 years)
- 232 subjects with ‘normal’ kidney function
- Emory; U. of Alabama; Kansas University; Mayo

Kidney International, 64: 2214–2221, 2003*

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**CRISP Results**

- **Total Kidney Volume (TKV)** increased over the three-year interval +204 ml ± 246 (n= 214, P< .001) and **Total Cyst Volume (TCV)** increased +218 ml ± 263 (n= 210, P < .001).

- There was a direct correlation (r=0.95, P < .001) between the rate of change in TKV and the rate of change in TCV.

- The change of volume in the left kidney correlated directly with the change in the right kidney (r=0.67, P<.001).

*New England J. of Medicine 354(20):2122-30*
The difference between TKV and TCV (non-cyst volume, NCV), was 540.1 ml ± 179.8.

Figure 1. Combined left and right kidney (A) and cyst (B) volumes in relation to age in women (blue) and men (red).

Figure 3. Relation between changes in TKV and TCV over three years for individual subjects. B. Relation between kidney volume changes in left and right kidneys over three years for individuals. Lines of identity are shown.
..... the rates of volume increase, determined from the annual measurements of TKV, were not different between left (5.1%/year ± 4.5) and right (5.4%/year ± 4.4) kidneys.

Glomerular filtration rate (GFR) declined only in those with the largest kidneys (>1500 milliliters).

This concept of progression of ADPKD has been validated! We now have a research tool to determine the progression of cystic kidney disease over a relatively short time period
## New Therapies On the Horizon

### Animal Studies
- Corticosteroids
- Paclitaxel (Taxol)
- Potassium bicarbonate or potassium citrate
- Lovastatin
- Inhibitors of Caspase
- PPARg (peroxisome proliferator) inhibitors

### Human Studies
- Inhibitor of EGFR tyrosine kinase activity (EKI-785)
- Sirolimus
- Angiotensin blockade
- Somatostatin
- Inhibition of vasopressin V2 receptor (OPC31260; OPC41061 (Tolvaptan))

## What is Vasopressin?
- Vasopressin is a hormone made by the pituitary gland in brain
- The primary function of vasopressin is to regulate how the kidney handles fluid
- Lack of vasopressin leads to excessive loss of fluid → urine output may exceed 10 quarts daily
- Too much vasopressin causes water intoxication
- Vasopressin increases the level of cyclic AMP in kidney cells

**cyclic AMP is one of the “bad actors” in ADPKD**
Hormone in blood (vasopressin)

Binds to receptor on surface of cell (vasopressin receptor)

Binding of hormone to receptor leads to change in cell chemistry (increased cyclic AMP)

Change in cell chemistry leads to change in cell function (water able to pass through kidney cells into blood)

Change in cell function leads to change in kidney function (concentrated urine and decreased urine production)

Hormone in blood (vasopressin)

Tolvaptan

Binds to receptor on surface of cell (vasopressin receptor)

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Change in cell chemistry leads to change in cell function (water able to pass through cells into blood)

Change in cell function leads to change in kidney function (concentrated urine and decreased urine production)
Pkd<sup>−/−</sup>m<sup>1So</sup>m mouse, orthologous to human PKD2; OPC31260 given between 3 and 16 weeks of age

Torres et al, Nature Medicine March, 2004

**Side Effects of Tolvaptan**

- Increased urine output: 4-5 quarts/day!!
- Thirst: must drink fluids to keep up!!

- Already well studied and found to be safe and effective in disorders of water retention:
  – congestive heart failure
  – cirrhosis of the liver
Tolvaptan in Human ADPKD

• Phase II studies (safety, dosing, side effects) completed
• Open label extension only for those subjects already participating (51 people)
• Plans for multicenter trial (phase III) being developed—late 2006
  – Assessment of change in kidney size over time as assessed by MRI versus kidney function
  – Side effects; tolerability; dose; safety

• 1-866-712-5837 for information (Otsuka)

What is the Renin-Angiotensin Axis (RAAS)?

• RAAS is a kidney hormone system that is designed to maintain blood flow and protect the kidney during times of low blood pressure/flow
• In response to reduced blood flow, the kidney makes the enzyme renin which converts angiotensin I to angiotensin II
• In all kidney diseases, including PKD, the RAAS is overactive
• Excessive activation of the RAAS system appears to be harmful……..see next slide
Effect of Angiotensin Blockade

- In animal models of PKD
  - Reduced kidney size by about 10-50%
  - Preserved kidney function
- In human kidney disease, other than ADPKD
  - Effective in slowing progression of kidney diseases typically associated with protein in the urine, diabetes and nephritis
  - Effective in slowing progression of kidney disease in African Americans with hypertension
- In ADPKD, has not been shown to slow progression of kidney disease. However, effective in preventing thickening of the heart muscle (LVH: left ventricle hypertrophy)
Limitations of Prior Studies of ACE-I in ADPKD

• TOO SMALL: No study sufficiently large enough to test effectiveness of RAAS blockade in ADPKD

• Is it safe?
  – Elevated potassium
  – Acute kidney failure (elevated serum creatinine) due to decreased blood supply to kidneys

• ?Adequate blockade of angiotensin II generation

Multilevel Blockade of the RAAS

- Angiotensinogen
- Renin
- Angiotensin I
- Angiotensin II
- Angiotensin II Receptor
- ACE
- ACE-I
- Chymase
- Others
- ARB
HALT-PKD
(Halt Progression of Autosomal Dominant Polycystic Kidney Disease)

Objective: Two concurrent, randomized, double-blinded controlled trials to assess the effects of multi-level blockade of the renin-angiotensin-aldosterone system (RAAS) and aggressive blood pressure control on progression of early (NKF Stage 1-2) and late (NKF Stage 3) ADPKD over a 5-year period (NCT00283686)

Hypotheses:
1) Blockade of RAAS will significantly reduce renal progression as compared to other antihypertensive therapy
2) Lower blood pressure will significantly reduce renal progression as compared to standard BP targets

Risks/Benefits of RAAS Interruption in ADPKD

Hypothesized benefits of RAAS Blockade in ADPKD
- Reduction of blood pressure
- Reduce pressure in kidney filters (glomerulus)
- Reduce excretion of protein in the urine
- Reduce production of molecules that cause scarring and inflammation of the kidneys

Risks of RAAS Blockade in ADPKD
- Ischemia – further reduction of blood flow already compromised by compression from expanding cysts
- Elevated potassium
- Acute renal failure: elevated creatinine
When to Treat and What to Measure?

Study A

Renal function (%)

Time

Study B

Summary of Interventions and Outcomes of Study A and B

<table>
<thead>
<tr>
<th>Baseline GFR (ml/min/1.73 m²)</th>
<th>Primary Outcome</th>
<th>Intervention</th>
<th>BP Target (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study A &gt;60</td>
<td>% Change in Total Kidney Volume by MRI</td>
<td>1. ACE + ARB</td>
<td>≤130/80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. ACE</td>
<td>≤130/80</td>
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<tr>
<td></td>
<td></td>
<td>3. ACE + ARB</td>
<td>≤110/70</td>
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<td>4. ACE</td>
<td>≤110/70</td>
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<tr>
<td>Study B 30-60</td>
<td>50% decrease in eGFR/ESRD/Death</td>
<td>1. ACE + ARB</td>
<td>≤130/80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. ACE</td>
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</tbody>
</table>
Inclusion Criteria

1. Diagnosis of ADPKD (may need to provide films)
2. Age:
   - Study A: 15-49 years
   - Study B: 18-64 years
3. Glomerular Filtration Rate (GFR)
   - Study A: >60 ml/min/1.73 m², from serum creatinine
     using the 4-variable MDRD equation
   - Study B: 30-60 ml/min/1.73 m²
4. Hypertension or high-normal blood pressure:
   >130/80 mm Hg
5. Informed consent

Exclusion Criteria

- <15 or >64 years of age
- absence of structural evidence of ADPKD
- GFR predicted out of targeted range:
  - for subjects 18-64, GFR <30 ml/min/1.73 m²
  - for subjects >49 years of age, GFR >60 ml/min/1.73 m²
- Spot urine albumin-to-creatinine ratio >0.5
- Absence of hypertension or high-normal BP
- Diabetes or HbA1C >6.5%
- Pregnancy or pregnancy anticipated over 5 years
- Congestive heart failure or >55 at high cardiovascular risk
- Serious other illness for which life expectancy <2 years
- Absolute need for beta-blocker or calcium channel blocker
- Prior allergic reaction due to ACE-I or ARB
Patient Follow-up

- Year one: 4 visits, screening, baseline, 4 and 12 months
- Year two onwards: study visits every 6 months
- Home BP measurement every month

- Study A only: Magnetic Resonance Imaging of total kidney volume/ Magnetic Resonance Angiogram of kidneys at baseline, 24, and 48 months

The HALT PKD Study has started!
HALT PKD Clinic Catchment Zones

Univ. Colorado
(Dr. R. Schrier)

Mayo Clinic
(Dr. V. Torres)

Tufts-NEMC
(Dr. R. Perrone)

Data Coordinating Center

Washington Univ.
(Dr. P. Miller)

haltpkd.org

HALT PKD Patient Care Centers

• 1-866-846-2735  Tufts-NEMC, Boston
• 1-866-650-1815  BIDMC, Boston
• 1-404-686-8280  Emory, Atlanta
• 1-888-630-2616  Mayo, Rochester
• 1-800-223-2273, Ext. 44680  Cleveland Clinic, Cleveland
• 1-913-588-7609  U. of Kansas, Kansas City
• 1-877-765-9297  U. of Colorado, Denver
Required Basic Information

Required Medical Records:
- Most recent serum creatinine, if available
- Ultrasound report or other diagnostic imaging report confirming ADPKD
- Documentation of high-normal BP or hypertension (current use of medications to control BP or $\geq130/80$ mm Hg on 3 separate occasions within the past year)

Somatostatin
- Octreotide: Sandostatin LAR Depot
- Given as a monthly injection (two injections, 20 mg per buttock)
- Blocks secretion of insulin and other hormones: used for rare endocrine tumors
- Side effects: diarrhea, abdominal pain, gallstones, rare allergic reactions
- Why use? Initially observed to slow cyst growth in a person with ADPKD; blocks cyclic AMP formation
- One study of 12 subjects with ADPKD: 6 months of treatment versus placebo
- Well tolerated in this pilot study
- Full scale trial planned in Italy NCT00309283
Sirolimus (Rapamycin)

- Found to inhibit cyst growth in several rat and mouse models of PKD
- Known to decrease proliferation (growth) of cells; very potent drug with many side effects
- FDA approved and presently used for transplant immunosuppression and coating of vascular stents
- 4 PKD patients who had transplants and received sirolimus had smaller PKD kidneys than 4 subjects treated with other medications (12 months after transplant)
Side Effects of Sirolimus

Sirolimus is a serious medication! The consequences of life-long use are undefined!

Clinical trial planned @ Cleveland Clinic
NCT00286156

• Elevated cholesterol
• Increased susceptibility to infection
• Impaired wound healing, post-op hernias
• Decreased platelets and white blood cells
• Long-term risk of malignancy perhaps less than for other immunosuppressive agents
The future is promising with lots of reason for optimism:

New research methodology to detect early progression

Clinical trials in progress

New therapies on the horizon