New treatments for Autosomal Dominant Polycystic Kidney Disease

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Faculty/Presenter Disclosure

• Faculty: Matthew Lanktree MD, PhD, FRCPC

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Objectives

- Summary of ADPKD
- Precision medicine approach to ADPKD
- Conservative treatments for ADPKD

Strategies currently under study:

- Vaptans (tolvaptan, lixivaptan)
- mTOR inhibitors (everolimus, sirolimus)
- Somatostatin (lantreotide, pasireotide, octreotide)
- Tyrosine kinase inhibitors (bosutinib, tesevatinib)
- Glucose metabolism (metformin, salsalate)
- Glucosylceramide inhibitor (venglustat)
- Bardoxolone
- Cyst sclerotherapy
ADPKD is bad luck

- ~1 in 1000
- 70% have kidney failure by age 70
Natural History of ADPKD

GFR: glomerular filtration rate.
Renal and Extrarenal Manifestations of ADPKD

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Incidence in adults with ADPKD</th>
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<tbody>
<tr>
<td>Hematuria</td>
<td>42%</td>
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<tr>
<td>Urine concentration defects</td>
<td>100%</td>
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<tr>
<td>Proteinuria</td>
<td>18%</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>19-40%</td>
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<tr>
<td>Hepatic cysts</td>
<td>85-94%</td>
</tr>
<tr>
<td>Intracranial aneurysms</td>
<td>5-10%</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>26%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>~100%</td>
</tr>
<tr>
<td>Renal function decline</td>
<td>~100%*</td>
</tr>
<tr>
<td>Hypertension before renal function decline</td>
<td>60-75%</td>
</tr>
</tbody>
</table>

*~70% of patients with ADPKD progress to ESRD at a median age of 58 years

Heritability of ADPKD

~10% of patients with ADPKD have *de novo* disease due to a spontaneous mutation
Variability in ADPKD severity

Cornec-LeGall et al., JASN 2016
Precision medicine?

- Classical definition of disease, family history
- Advanced genetic, imaging and biomarker data
- Patient values and preferences
- Stratify risk, maximize therapeutic potential while mitigating therapeutic burden
Conservative strategies

- Have plenty of vegetables and fruits
- Eat protein foods
- Make water your drink of choice
- Choose whole grain foods

- NO SMOKING

- Healthy lifestyle icons
WATCHING YOUR STEP – THE DIFFERENT STAGES OF CLINICAL DEVELOPMENT AND WHAT THEY EXAMINE

PHASE I
Checking for safety
Sample: 10-20 healthy volunteers
Unexpected side effects may occur

PHASE II
Checking for efficacy
Sample: about 200 patients
Most research projects fail in Phase II due to product not being as effective as anticipated

PHASE III
Confirm findings in large patient population
Sample: more than 1,000 people
Likelihood to detect rare side effects increases with number of people involved

PHASE IV
Testing long-term safety in diverse patient population
Sample: “real life patients” – testing being carried out outside of clinical environment (post-marketing studies)
Previously untested groups may show adverse reactions

Source: AGCS
Tolvaptan Mechanism of Action

- Vasopressin promotes cyst growth in the kidneys in patients with ADPKD

- Tolvaptan blocks these effects through inhibition of the vasopressin V2 receptor
Tolvaptan: 1-year change in kidney function

Tolvaptan slowed the rate of kidney function decline by 35% over 1 year compared to placebo.

Change in eGFR mL/min/1.73m²/yr

Tolvaptan

Placebo

Difference: 1.271 mL/min/1.73m²/yr (35%)
p-value; <0.0001

Adjusted by the duration of the trial for each patient
ELiSA trial: Lixivaptan

- Same mechanism of action as tolvaptan
- Avoid liver toxicity, less blood work?
- Currently in phase II, end Sept 2019
mTOR inhibitors

- Everolimus (Affinitor), sirolimus (Rapamune)
- Immunosuppressant post kidney transplant
- Cancer treatment
- Tuberous sclerosis complex
- Cardiac stents
- Worked well in pre-clinical studies
- 3 negative trials in ADPKD
- Dose limited by side effects?
Somatostatin

• Inhibitory hormone secreted by gut
  • Decrease growth hormone, prolactin, insulin and glucagon
  • Decrease thyroid stimulating hormone
  • Decrease cAMP
  • Slows movement of food through intestines

• Analogs: octreotide, lanreotide, pasireotide

• Promising in pre-clinical animal studies and small Phase II clinical trials
Can Lanreotide slow the progression of autosomal dominant polycystic kidney disease? The DIPAK1 trial

**Randomization**
- Open label RCT
- 4 Outpatient clinics
- n = 309
- eGFR 30-60 ml/min
- ADPKD
- Age 48.4 yrs
- Women 53.4%

**Primary Outcome**
- eGFR Decline
- -3.46 ml/min/yr (-3.9, -3.0)

**Secondary Outcome**
- Kidney Volume Growth
- 5.5% Per yr
- Quality of life
- 0.07 Composite Score

**Randomized**
- Standard care
  - n = 154
  - Age 50 yrs
  - Women 57.9%
  - ADPKD
- Lanreotide + Standard care
  - n = 155
  - Age 50 yrs
  - Women 59.3%
  - ADPKD

- NS
- p = 0.02
- NS

Conclusion: Lanreotide was not effective in slowing the decline in kidney function in patients with later-stage ADPKD over 2.5 years of follow-up


@divyaa24
Tyrosine kinase inhibitor in Phase II

**Bosutinib (BOS) vs. Placebo for ADPKD**
Phase 2, Multisite Study

<table>
<thead>
<tr>
<th>Outcomes (treatment for 2-24 wks)</th>
<th>Placebo N = 56</th>
<th>BOS 200 mg/d N = 58</th>
<th>BOS 200/400 mg/d N = 34</th>
<th>BOS 400 mg/d N = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized rate of kidney enlargement</td>
<td>4.74 %</td>
<td>1.63 %</td>
<td>-0.2 %</td>
<td>1.29 %</td>
</tr>
<tr>
<td>Annualized eGFR decline rate (ml/min/1.73 m$^2$)</td>
<td>-2.54 %</td>
<td>-3.09 %</td>
<td>-4.76 %</td>
<td>-7.43 %</td>
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**CONCLUSION:** Compared with placebo, bosutinib at 200 mg/d reduced kidney growth in patients with ADPKD ($p = 0.01$), thought the eGFR decline rate was similar ($p = 0.71$).

August 24, 2017
The Warburg Effect
Inhibition of aerobic glycolysis

• Metformin
  • Baltimore: ongoing; placebo; 100 patients; end December 2020
  • Colorado: ongoing; placebo; 50 patients; end March 2020
  • Italy: enrolling; vs. tolvaptan; 150 patients; end Jan 2022

• Pioglitazone
  • Indiana: ongoing; 18 patients; end Oct 2020

• Salsalate (NOT salicylate, ASA, aspirin)

• Intermittent fasting
  • Colorado: recruiting; 40 obese patients; end Sept 2020
Glucosylceramide inhibitor (Venglustat)

- Used to treat Fabry & Goucher disease

- Multi-national Phase II trial 560 patients now enrolling
Bardoxolone

- Activator of Nrf2 pathway (increases production of anti-oxidants)
- Nrf2 is suppressed in chronic inflammation
- Studied in diabetic nephropathy, Alport syndrome, nephrotic syndrome, IgA nephropathy
- Largest trial stopped early due to concern about cardiac toxicity
- One trial in ADPKD ongoing, expected end August 2019
Cyst sclerotherapy

• Interventional radiology procedure
• >5 cm cysts
• Sodium tetradecyl sulphate (STS)
Statins

• Lower LDL cholesterol, reduce inflammation
• One trial suggested benefit in pediatric population
• Already at elevated cardiovascular risk
• One trial recruiting in Colorado, 250 patients, expected end date December 2021
Water prescription

• Inhibit vasopressin secretion
  • as opposed to blocking vasopressin action like tolvaptan

• When water can be bad?

• PREVENT-ADPKD: multi-national Australian led
  • 3 years, recruiting now, 180 patients; usual vs. prescribed water intake

• DRINK trial: UK
  • 8 weeks, done, 42 patients, feasibility study
Conclusions

• Precision medicine
• Conservative measures
• Tolvaptan?
• More to come...

Vaptans (tolvaptan, lixivaptan)
mTOR inhibitors (everolimus, sirolimus)
Somatostatin (lantreotide, pasireotide, octreotide)
Tyrosine kinase inhibitors (bosutinib, tesevatinib)
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