Modern Management of Polycystic Kidney Disease

Rationale, tools and management of ADPKD in the KCC

Mike Bevilacqua
Nov 29, 2018
Outline

New insights into ADPKD and Rationale for an ADPKD clinic

• Better understanding of PKD
• New tools and treatments for PKD

Goals and anticipated management of ADPKD within the KCC

• Current state of PKD in BC
• Alignment of PKD care with KCC framework
• Best practices development and working group
Disclosures

Relevant to this topic, I disclose the following from Otsuka Canada Pharmaceuticals Inc:

• An unrestricted grant to the BCPRA to assist in creation of the PKD registry
• Honoraria for participation in advisory boards, consultancy groups and development of educational material related to PKD
Epidemiology

• Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, affecting between 1-2.5/1000 live births
  – Although exact provincial numbers are lacking, this estimate would mean there are somewhere from 4600 to over 10000 British Columbians living with the disease.

• Of patients with an identifiable etiology of ESRD, ADPKD is the 4th leading cause of ESRD in Canada
ADPKD is a more complex disease than previously appreciated
Different faces of PKD
It gets more complicated...

There are a huge number of individual mutations, many of uncertain prognostic significance

**Mayo PKD mutation database**

- PKD1 – 2323 known mutations, 868 clear pathogenic significance
- PKD2 – 278 mutations, 168 clear pathogenic significance

In any case, genetics only tells you about average disease course, not your individual patient
The disease course is variable one, with the early disease marked by cyst proliferation and expansion with little renal dysfunction followed by a precipitous decline. The corollary here is that by the time there is a change in GFR, significant cyst expansion and proliferation has already occurred.
A good way to conceptualize this is to think of diabetic nephropathy. Upwards of 5ml/year decline in GFR is observed.

Maintained GFR in the setting of renal parenchymal loss = hyperfiltration.

The disease course is variable, with the early disease marked by cyst proliferation and expansion with little renal dysfunction followed by a precipitous decline. The corollary here is that by the time there is a change in GFR, significant cyst expansion and proliferation has already occurred.
Tools to evaluate ADPKD are becoming more specialized
Changes in kidney size precede change in renal function

Significant changes in kidney volume can be detected years before changes in GFR

Figure 2. Average standardized change in hTKV and iothalamate GFR. hTKV determined at baseline and iothalamate GFR at baseline and five subsequent visits until year 8 (n=93 with complete data). P<0.01 based on paired t test comparing each year to baseline for hTKV (*) and GFR (#). hTKV, height-adjusted total kidney volume.

TKV-based prognostication: the Mayo classification

At present this appears to be the most robust individualized predictor of early stage progression in PKD patients (i.e., before GFR declines)
Mayo classification categorizes rate of kidney growth

<table>
<thead>
<tr>
<th>Class</th>
<th>Average annual change in TKV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>&lt;1.5%</td>
</tr>
<tr>
<td>1B</td>
<td>1.5-3</td>
</tr>
<tr>
<td>1C</td>
<td>3-4.5</td>
</tr>
<tr>
<td>1D</td>
<td>4.5-6</td>
</tr>
<tr>
<td>1E</td>
<td>&gt;6%</td>
</tr>
</tbody>
</table>

The 1A-1E classification is best thought of as a *velocity of growth classification* – the classes refer to the average annual growth in htTKV.
Mayo class predicts rate of GFR loss

<table>
<thead>
<tr>
<th>Class</th>
<th>Average annual change in TKV</th>
<th>Average annual decrease in eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>&lt;1.5%</td>
<td>0.23</td>
</tr>
<tr>
<td>1B</td>
<td>1.5-3</td>
<td>1.33</td>
</tr>
<tr>
<td>1C</td>
<td>3-4.5</td>
<td>2.63</td>
</tr>
<tr>
<td>1D</td>
<td>4.5-6</td>
<td>3.48</td>
</tr>
<tr>
<td>1E</td>
<td>&gt;6%</td>
<td>4.78</td>
</tr>
</tbody>
</table>

The average GFR comes from >8 years of CRISP and Mayo clinic follow-up data
ADPKD carries a higher disease burden than is recognized.
Extra-renal manifestations of PKD

**KIDNEY-RELATED**
- Pain and discomfort
- Kidney stones
- Cyst bleeds
- Infected cysts
- High blood pressure
- Blood in urine
- Worsening kidney function / kidney failure

**NON-KIDNEY-RELATED**
- Brain aneurysm*
- Cardiovascular* (e.g., heart valve problems)
- Liver cysts
- Hernias of the abdomen
- Diverticulosis* (outpouchings of the large intestine)
- Seminal vesicle cysts

Not everybody with ADPKD will experience all of these complications.

ADPKD: Autosomal Dominant Polycystic Kidney Disease
Other complications of PKD

Pain, hematuria, infection and stones can occur early in the disease course

- Up to 25% of PKD patients present with these symptoms in the setting of preserved renal function
- The occurrence of these symptoms does not completely coincide with their renal disease course

By age 30, over 50% have at least one complication


Abdominal symptoms

Over ¼ of people with GFR >60 have abdominal symptoms related to their PKD
Patient perspectives of PKD

The physical symptoms and complications are only one aspect of the total burden of PKD.

Treatments for ADPKD are becoming more specialized
Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D.,
Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D.,
Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D.,
Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D.,
for the TEMPO 3:4 Trial Investigators*

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D.,
Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D.,
Ronald D. Perrone, M.D., Gary Koch, Ph.D., John Ouyang, Ph.D.,
Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S. Czerwiec, M.D., Ph.D.,
and Olga Sergeyeva, M.D., M.P.H., for the REPRISE Trial Investigators*
How tolvaptan (vasopressin 2 receptor antagonist) works
Results in early(earlier) stage patients

Increase in TKV was 2.8%/year (2.3-3.1%) in the tolvaptan group vs. 5.5%/year (5.1-6.0%) in the placebo group.
Results in early(earlier) stage patients

Slope of reciprocal of creatinine (which varies directly with GFR) was -2.61/year compared to -3.81/year in the placebo group. This corresponds to a GFR slope of -2.72ml/min/year vs. -3.70ml/min/year
Results in later stage patients

Tolvaptan vs Placebo

Placebo off-tmt (Avg of 3 samples)

Tolvaptan (tolvaptan run-in)

Placebo (tolvaptan run-in)

Tolvaptan off-treatment baseline (Avg of 3 samples)

Visit (Month)

Change from Pre-treatment Baseline (CKD-EPI: mL/min/1.73m²)

LS Mean Annualized Change in eGFR (± SE) (CKD-EPI: mL/min/1.73m²/yr)

Tolvaptan vs Placebo

Difference: 1.271 mL/min/1.73m²/yr (35%)
p-value: <0.0001
Adverse effects - aquaretic symptoms

This is a difficult drug for patients to work into their lives.

- It induces a different disease to slow the existing one

- There is a high rate of side effects and discontinuation
Dealing with aquaretic symptoms

• Judicious approach to dose titration

• Minimizing dietary solute intake (primarily salt and protein)

• Treat this like a ‘sick day’ medication - or more accurately, a ‘convenience day’ or ‘cheat day’ medication
Increased transaminases and need for monitoring

- Overall, there is a 4-5% rate of increased liver enzymes with tolvaptan
  To compare to other drugs associated with AST/ALT increases:
  - INH: up to 20%
  - MTX: 15%
  - Amiodarone: 3-6%
  - Lipitor: <2%

- But in the trials, 3 patients had AST/ALT >3xULN and bilirubin >2xULN.
  - Signal of much worse liver injury called Hy’s Law

- The injury is reversible with drug discontinuation

- There is mandatory hepatic monitoring while on tolvaptan (monthly at first then q3 months)
A new management paradigm for ADPKD
Targeted and non-target treatments

Recent Advances in the Management of Autosomal Dominant Polycystic Kidney Disease
Foad T. Chebib and Vicente E. Torres

Basic optimized ADPKD management
- Blood pressure control (Goal ≤ 110/75 mmHg if 18-50 y.o. and eGFR > 60 ml/min; otherwise ≤ 130/85 mmHg)
- Maintain UOsm ≤ 280 mOsm/kg by moderately enhancing hydration spread out over 24 hrs (during the day, at bedtime and at night if waking up)
- Low osmolar intake: Moderate sodium (2.3-3g/d), moderate protein (0.8-1 g/Kg of ideal body weight)
- Maintain serum bicarbonate ≥ 22 mEq/L; moderate dietary phosphorus (800 mg/d)
- Moderation of caloric intake; maintain normal BMI; exercise
- Lipid control; low threshold to start statins (aim for LDL ≤ 100 mg/dL)
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Goal</th>
<th>Methods to Achieve Goal</th>
<th>Evidencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive BP control</td>
<td>≤110/75 mm Hg in: 1. 18-50-year-olds 2. GFR=60 ml/min per 1.73 m² 3. Particularly Mayo Clinic class 1C-E Intracranial aneurysm Valvular heart disease</td>
<td>Early detection is essentialb</td>
<td>Grade 1B</td>
</tr>
<tr>
<td>Sodium</td>
<td>≥130/85 mm Hg in: 1. Other adult hypertensives Moderate restriction (2.3–3 g/d) Adjust for extrarenal losses (hot climate, runners, sauna, bowel disease) if appropriate</td>
<td>Counseling</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Hydration</td>
<td>Moderately enhanced hydration spread out over 24 h (during the day, at bedtime, and at night if waking up) Maintain urine osmolality ≥280 mOsm/kg</td>
<td>Monitor 24-h urine sodium Counseling</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Protein</td>
<td>0.8–1.0 g/kg of ideal body wt</td>
<td>Diets contain protein: 0.6 g/(urine urea nitrogen in g/d + 0.03 [weight in kilogram]) Use of phosphate binders not different from other advanced CKD when needed</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Moderate diet phosphate restriction (800 mg/d)</td>
<td>Diets contain phosphates</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Acid base</td>
<td>Maintain plasma bicarbonate within the normal range (≥22 mEq/L)</td>
<td>Increase fruits/vegetables (2–4 cups/d) Oral sodium bicarbonate if needed</td>
<td>Grade 2B</td>
</tr>
<tr>
<td>Caloric intake</td>
<td>Maintain normal BMI Moderation in caloric intake</td>
<td>Diets with saturated fats and cholesterol</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Lipid control</td>
<td>Aim for serum LDL ≤100 mg/dl</td>
<td>Dietary follow-up</td>
<td>Grade 2B</td>
</tr>
</tbody>
</table>

ADPKD, autosomal dominant polycystic kidney disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; BMI, body mass index.

aGrading of levels of evidence is provided in Supplemental Table 1.
bScreen children at risk every 3 years starting at age 5 years. Children with hypertension should be referred and managed by experts in pediatric hypertension.
Other targets in PKD
Let’s confirm the diagnosis and then we will tell you about screening your family members.

Drink lots of water, keep your blood pressure in the normal range and do your bloodwork. See you back in 6-12 months.

When your GFR drops, we’ll start talking about transplant and dialysis.

What we have done with PKD in the past
What we need to do with ADPKD now

Tell us what your family screening, reproductive, financial, symptom and renal failure concerns are and we will discuss those.

We will use imaging and other tools to more accurately predict your renal progression.

We will discuss conventional treatments like BP reduction that apply to everyone with PKD and will also assess whether you are a candidate for new disease specific treatments.
PKD patients in BC that we know of (ADPKD registry)
Many of the patients identified are early stage
Many are in KCC, more are not

71  68
39  42
8   8
253 251
235 257
318 323

HD    PD    HHD    Tx    KCCs    Private offices
Apr-18  Sep-18

HD: 71 (Apr) 68 (Sep)
PD: 39 (Apr) 42 (Sep)
HHD: 8 (Apr) 8 (Sep)
Tx: 253 (Apr) 251 (Sep)
KCCs: 235 (Apr) 257 (Sep)
Private offices: 318 (Apr) 323 (Sep)
Modern management of ADPKD aligns with goals of KCC

- Early identification and care
  - All documents (KCC best practices, ADPKD guidelines) suggest early referral

- Evaluation of risk of progression, implementation of tailored treatment strategies

- Interprofessional programs focusing on different aspects of the disease process and experience

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**Table 2. Basic optimized management of adult patients with ADPKD**

<table>
<thead>
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<th>Intervention</th>
<th>Goal</th>
<th>Methods to Achieve Goal</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP control</strong></td>
<td>Early detection is essential&lt;sup&gt;5&lt;/sup&gt;</td>
<td>By order of preference: 1. ACE/ARB 2. ARB/or cardioselective β-blocker 3. Dihydropyridine CCB 4. Diuretics&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Grade 1B</td>
</tr>
<tr>
<td><strong>Sodium</strong></td>
<td>Counseling</td>
<td>Dietary approach to stop hypertension (DASH)-like diet at early stages</td>
<td>Grade 1C</td>
</tr>
<tr>
<td><strong>Hydration</strong></td>
<td>Monitor 24-h urine sodium</td>
<td>Monitor 24-h urine sodium</td>
<td>Grade 1C</td>
</tr>
<tr>
<td><strong>Phosphorus</strong></td>
<td>Maintain normal BMIs; limitation in caloric intake</td>
<td>Dietetic follow-up</td>
<td>Grade 1C</td>
</tr>
<tr>
<td><strong>Lipid control</strong></td>
<td>Aim for serum LDL &lt;100 mg/dL</td>
<td>Regular exercise</td>
<td>Grade 2B</td>
</tr>
</tbody>
</table>

ADPKD, autosomal dominant polycystic kidney disease; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; BMI, body mass index.

<sup>5</sup>Coding of levels of evidence is provided in Supplemental Table 1.

<sup>6</sup>Screens children at risk every 3 years starting at age 3 years. Children with hypertension should be referred and managed by experts in pediatric hypertension.
Coming soon: Best practices for management of ADPKD in the KCC

• Goal will be a complement to existing best practices
• How to implement modern treatment strategies within the KCC
• Not a standalone document, not meant to be a standalone clinic

SHAMELESS PLUG

• Working group formed, but we would love to have you!
  • Email me if you would like to join
• Seeking multidisciplinary input, involvement from across the province
Summary

• Our understanding of ADPKD is evolving, new treatment strategies

• Modern management includes predicting risk of progression, tailoring treatments

• There are a host of management strategies encompassing many dimensions of care to consider in ADPKD

• The KCC framework is well suited to these needs, with some specific adjustments for ADPKD patients
  • Stay tuned for the best practices document and let me know if you want to be involved!
Questions/comments