Research Update: Assessing ARPKD Kidney and Liver Disease Progression

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Overview

- Why is it important to measure ARPKD kidney and liver disease progression?
- How do we currently measure ARPKD kidney disease progression?
- How do we currently measure ARPKD liver disease progression?
- Are there newer ways to ARPKD progression?
- What is MRI “fingerprinting” and why is it important?
- Future directions?
Why is it important to measure ARPKD kidney and liver disease progression?

- It allows treating physicians to assess where the disease is at the moment and how quickly it is getting worse.
- It allows researchers to assess the effects of a drug or other intervention in a clinical trial (study “endpoints”).
- Since those trials typically last 2-5 years, these “endpoints” need to be expected to change during the course of the study in order for meaningful comparisons to be made between the treatment and “control” groups.
- There are several experimental medications that have been shown to slow disease progression in ARPKD animal models and some of those medications (such as Tolvaptan) have been studied in adult ADPKD patients. We want to be able to study those medications in ARPKD patients as well.

How do we currently measure ARPKD kidney disease progression?

- Standard clinical measures of kidney disease progression include:
  - Serum creatinine
  - Estimated glomerular filtration rate (GFR) (“Schwartz formula” in children, CKD-EPI formula in adults)
  - Measured GFR (e.g. iohexol or iothalamate clearance)
  - Urine protein measurements
  - Kidney ultrasound and other imaging
- The Food and Drug administration (FDA) currently only accepts a significant (usually 30-50%) reduction in GFR or a doubling of serum creatinine as an endpoint for clinical trials of CKD – but PKD researchers and others are trying to change that and have them accept other “surrogate markers” (such as MRI measures of total kidney volume in ADPKD)
**ARPKD kidney disease progression: Insights from the CKiD Study**

- Chronic Kidney Disease in Children (CKiD) is a multi-center longitudinal, prospective study of CKD in children.
- More than 50 pediatric nephrology centers in the US and Canada participate and over 800 children are enrolled.
- To enter the study, patients had to be 1-16 years of age, with an estimated GFR of 30-90 ml/min/1.73m2 and cannot have had a prior transplant (kidney, liver, heart or bone marrow).
- The 4 major areas of focus are kidney disease progression, growth, neurocognition and cardiovascular health.
- Patients have yearly visits until if they reach end-stage renal disease, then are followed by phone follow up visits yearly.
- The study is now in its 10th year and is currently closed for enrollment but may re-open for young children (<5 years old) in the near future.

**CKiD ARPKD Kidney Disease Progression Study**

- Examined data from the 22 ARPKD patients enrolled in CkiD
- Primary outcome measure was change in measured GFR over time
- Secondary outcome measures were blood pressure control and protein in the urine
- ARPKD patients were also compared to two other groups of children with congenital kidney diseases
- In a separate study, neurodevelopmental aspects were studied (led by Dr Erum Hartung) and a study of growth is in submission.
Results

- ARPKD subjects, on average, had a relatively slow (6%) decline in GFR per year, *but the rate of decline varied considerably*. This rate of decline was similar to the other two groups studied.
- GFR declined faster in older children.
- ARPKD subjects had more severe high blood pressure, as evidenced by the need for more blood pressure medication – over 30% were on 3 or more medications.
- ARPKD subjects, even those with advanced CKD, had very little protein in their urine.

Conclusions

• This was the first study to prospectively assess kidney disease progression using measured GFRs in a well-characterized group of ARPKD patients

• Given the relatively slow rate of decline in GFR (in this study population) and the large variability from patient to patient, GFR decline alone would not be an adequate measure to use in a clinical trial to assess the effect of a medication or other treatment

  *We need a better kidney progression measure!*

How do we currently measure ARPKD liver disease (CHF) progression?

• **Standard clinical blood tests** such as bilirubin, AST/ALT or GGT are used commonly to assess liver disease, but are often normal in ARPKD patients, even when the disease is severe.

• **Liver biopsy** confirms the diagnosis of CHF but is invasive and not useful/practical for measuring the effect of a treatment over time

• **Endoscopy (EGD)** is used to assess for varices, but is not useful/practical for measurements over time
How do we currently measure ARPKD liver disease (CHF) progression?

Ultrasound elastography (“Fibroscan©”)

• Provides an assessment of liver stiffness and is good for distinguishing mild vs. severe disease.

• A small study of 7 ARPKD patients showed that it could detect fibrosis (Kummer et al Pediatric Nephrology 2011).

• Ultrasound elastography is currently being evaluated in larger number of ARPKD children in a separate study headed by Dr. Hartung.

• But it may not be sensitive enough to measure changes in CHF over a 3-5 year period of a clinical trial.

_We need alternative/complementary liver disease progression measures!

Why MRI?

• MRI is non-invasive and provides excellent visualization of difference between tissues/structures within the kidneys or liver.

• Unlike CT, there is no radiation.

• Many quantitative techniques (such as T1 and T2 relaxometry measurements) do not require gadolinium, which is an MRI IV contrast that can cause severe problems in patients with low GFRs.

• MRI results are generally very well-reproducible and most quantitative measurements can be done on standard clinical MRI scanners (no special equipment)

• MRI can be used to assess changes over time.

• MRI can be used to study animal models
Standard Clinical MRI Assessments of ARPKD and Liver Kidney Disease

**A**

**MEASURES:** Total kidney volume only; No specific measurements of the proportion of kidney cysts/abnormal kidney tissue

**B**

**MEASURES:** Overall appearance of liver and measurement of spleen size (to detect portal hypertension); No specific measurements of bile duct dilatation or scarring/fibrosis

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Measures of Kidney Disease in an ARPKD Animal Model: T2w-derived renal cystic burden

- **T2 IMAGES**
  - 1 month
  - 2 month
  - 3 month

- **T2 MAPS**
Measures of Liver Disease in an ARPKD model: T1 relaxation times

Gao et al, NMR Biomed Jan 2016

MRI assessments correlate with histologic measures of ARPKD Kidney and Liver disease

Gao et al, NMR Biomed Jan 2016
MR Fingerprinting:
What is it and why is it important?

- Quantitative MRI studies are lengthy (45-60 minutes) and require patients to remain still to avoid respiratory motion artifacts.
- Younger children (<8-10 years) typically require sedation/general anesthesia for those MRIs, which increases the risk and cost of the studies.
- These factors limit the use of MRI in clinical studies involving young children and is likely to limit their ability to participate in clinical trials that use MRI.
- The MRI research team at our institution pioneered a transformative MRI methodology, called Magnetic Resonance Fingerprinting (MRF), which can rapidly generate information (such as T1 and T2 relaxation time maps) and is resistant to motion artifact.
**MRF is resistant to motion and rapid**

12 seconds  
15 seconds

MRF derived T1 Map

MRF derived T2 Map

(From Ma D, et al Nature 2013)

**Kidney MRF**

MRF Image  
T1 Map Derived from MRF
Future Directions/Goals

• Clinical MRI studies in ARPKD patients to assess kidney and liver disease measures at baseline and over time
• Optimization of MRF in ARPKD kidney and liver disease in animal models
• Application of MRF to ARPKD patients
• Clinical trials of medications in ARPKD patients

Acknowledgements

Chris Flask (co-PI)
Dell/Flask Labs
Ying Gao
Christian Anderson
Lan Lu
Miwa Goto
Nita Hoxha
Jose Mariappurum

Collaborators/Advisors
John Sedor
CWRU Kidney Research Group
Erum Hartung
CKiD investigators and patients
Rebecca Wells
Ellis Avner
Lisa Guay-Woodford