ARegPKD-Newsletter 2014

1. What is the status of the registry?

The international ARPKD registry-study has been initiated by the German Pediatric Nephrology Association (GPN) and the European Study Consortium for Chronic Kidney Disorders Affecting Pediatric Patients (ESCAPE-Network). Since the launch of www.aregpkd.org 49 centers from multiple European countries, including France, Belgium, Turkey, Poland, Hungary, Italy, Lithuania, Spain, the Czech Republic and Germany have registered and we are expecting the inclusion of further centers. Patient informations and Informed Consent Forms are already available in English, Italian, Polish, Lithuanian, French and German. Forms in additional languages are underway. Many of the registered centers are currently applying for local Ethics Committee Statements. The first 77 patients have been included into the registry and the first biosamples have been collected. We expect to increase both numbers substantially within the next months.

2. What are other important PKD news?

A Clinical Consensus Recommendations Conference on ARPKD in Washington in May 2013

In May 2013 a Clinical Consensus Recommendations Conference exclusively devoted to patients with ARPKD took place in Washington D.C., USA. International experts, both from Europe and the US, met for two days to discuss clinical approaches for patients with ARPKD. After extensive literature review the main topics were first discussed in Working Groups focussing on Renal and Genetic, Neonatal, Hepatic, or Neurocognitive aspects of ARPKD. The results of these Work Groups were in a second step presented to and discussed among the attendees. A summarising manuscript was published in the *Journal of Pediatrics* in 2014 (Guay-Woodford LM et al., Consensus Expert Recommendations for the Diagnosis and Management of Autosomal Recessive Polycystic Kidney Disease: Report of an International Conference. The Journal of Pediatrics. 2014 Sep;165(3):611-7.) .

KDIGO (Kidney Disease / Improving Global Outomes) Controversies Conference on ADPKD in Edinburgh in January 2014

In January 2014 a KDIGO Controversies Conference on ADPKD took place in Edinburgh. International experts, both from Europe and the US, met for three days to discuss approaches for patients with ADPKD. Working Groups focussed on Diagnosis, Management of Renal Manifestations, Management of Hypertension and Renal Function Decline, Management of End Stage Renal Failure in ADPKD, Management of Extra-Renal Complications, and Practical Integrated Patient Support. The results of these Work Groups were in a second step presented to and discussed among the attendees.

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

(Torres VE et al. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2012 Dec 20;367(25):2407-18)

Torres et al. published the data of a phase 3, multicenter, double-blind, placebo-controlled 3-year trial, in which patients with ADPKD and an estimated glomerular filtration rate of >=60 ml/min received either tolvaptan – a V2-receptor antagonist - or placebo (TEMPO trial). Animal studies have convincingly shown that vasopressin promotes cyst proliferation and that vasopressin suppression decreases cyst proliferation.

In this trial tolvaptan slowed the increase in total kidney volume compared to placebo. Tolvaptan was also associated with lower rates of kidney pain as well as a slower decline in kidney function. However, thirst and polyuria occured as aquaresis-related adverse events; remarkable are transitory elevations of transaminases in patients treated with tolvaptan. In summary, this trial is the first to show a beneficial effect of pharmacological ADPKD treatment.

Still, there are considerable side effects and treatment is very expensive. Importantly, tolvaptan has not yet been approved for treatment of patients with ADPKD neither by the U.S. Food and Drug Administration nor by the European Medicines Agency.

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Somatostatin Analogue in Patients with Autosomal Dominant Polycystic Kidney Disease

(Caroli A, Perico N et al., Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. Lancet 2013; 382:1485-95)

The group published data from a multicenter, randomised, single-blind, placebo-controlled 3-year trial, in which adult patients with ADPKD and an estimated glomerular filtration rate of > 40 ml/min per 1,73 m² received either the somatostatin analogue octreotide long acting release or placebo. In-vitro studies suggested that transepithelial secretion of fluid in cysts is controlled by cyclicAMP (cAMP). Somatostatin is thought to inhibit adenyl cyclase and therefore to reduce cAMP.

In the mentioned trial octreotide-LAR reduced the mean increase of total kidney volume compared to placebo; while the effect was statistically significant for the 1 year follow-up, the significance got lost for the 3 year follow-up. Serious adverse events were similarily contributed to both groups, but 4 cases of biliary complications with cholelithiasis or acute cholecystitis occurred in the octreotide-group and were probably treatment-related.

Pravastatin in Pediatric Patients with Autosomal Dominant Polycystic Kidney Disease

(Cadnapaphornchai MA, George DM et al., Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2014 May;9(5):889-96)

This group conducted a double-blind placebo-controlled phase III clinical trial on 110 pediatric participants with ADPKD and normal kidney function receiving lisinopril who were randomised to treatment with pravastatin or placebo for a 3-year period with evaluation at 0, 18, and 36 months. The percent change in height-corrected total kidney volume adjusted for age, sex, and hypertension status over the 3-year period was significantly decreased with pravastatin; fewer participants receiving pravastatin experienced a more than 20% change of height-corrected total kidney volume compared to patients receiving placebo. The authors conclude that pravastatin may be an effective agent to slow progression of structural kidney disease in children and young adults with ADPKD. These findings support further investigation of a potential early intervention with pravastatin in ADPKD.

Primary Cilia as Specialized Calcium Signalling Organelles

(DeCaen PG, Delling M et al.,, Direct recording and molecular identification of the calcium channel of primary cilia . Nature 2013; 504(7479):315-8.

Delling M, DeCaen PG et al., Primary cilia are specialized calcium signalling organelles. Nature 2013; 504(7479):311-4.)

The exact cellular function of the two proteins affected in ADPKD remains incompletely understood. It has been suggested that the two proteins may serve as mechanosensors at the primary cilium of renal tubular cells and that renal tubular flow may modulate intracellular calcium levels via the polycystins. The laboratory of David Clapham now published data that describe cilia as calcium signalling organelles regulated by proteins of the polycystin family, namely PKD1L1 and PKD2L1. The authors show that changes in ciliary calcium levels do not result in relevant changes in cytoplasmatic calcium levels but that they do affect one of the major intracellular signalling pathways associated with monocilia, namely Sonic Hedgehog Signalling.