Effect of Tolvaptan in combination with rapamycin in a rat model of polycystic kidney disease

Authors
Maria Ougaard, Stine Jansen, Louise Thisted, Frederikke Sembach, Marie Rosenkilde, Michael Christensen

Gubra, Hørsholm, Denmark

Corresponding author
Michael Christensen mch@gubra.dk

Background & Aim

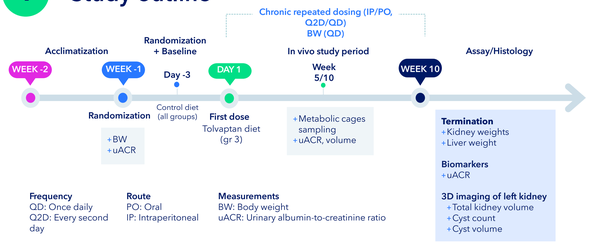
Polycystic kidney disease (PKD) is a congenital fibrocystic disorder where cysts are forming within the kidney and liver, causing declined kidney function and can eventually lead to chronic kidney disease (CKD). Animal models with improved clinical translatability can optimally inform about potential clinical efficacy of novel drug candidates for PKD. The PCK rat is an established genetic model of PKD with natural history and renal histologic abnormalities resembling the human disease.
Here, we characterized the effect of the vasopressin V2 receptor antagonist Tolvaptan, the only approved drug treatment for PKD, in combination with rapamycin, a compound known to slow cystogenesis in the PCK rat model.

Methods

Male PCK rats (PCK/CrljCrl-Pkhd1pck/Crl, Charles River Laboratories) arrived at 4 weeks of age. Male Sprague-Dawley rats served as healthy controls. PCK rats were randomized into groups based on body weight and urine albumin-to-creatinine ratio (uACR). PCK rats daily received vehicle, or Tolvaptan (in diet, ad libitum) + rapamycin (0.15 mg/kg, IP) every third day. Urine was collected in week 5 and 10 for uACR analysis. Upon termination, kidney and liver weight was obtained. Cyst counts and volume in the left whole-kidney were assessed quantitative 3D light sheet imaging. Data is presented as mean + S.E.M.

www.gubra.dk

1 Study outline



Group	Animal	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	SD rat	8	**Vehicle**	In diet + IP	Q3D	5 ml/kg	NA
2	PCK rat	9	**PCK vehicle**	In diet + IP	Q3D	5 ml/kg	NA
3	PCK rat	9	**PCK - Tolvaptan + Rapamycin**	In diet + IP	Ad libitum/Q3D	5 ml/kg	0.01% diet + 0.15 mg/kg

2 Body weight, kidney and liver weight

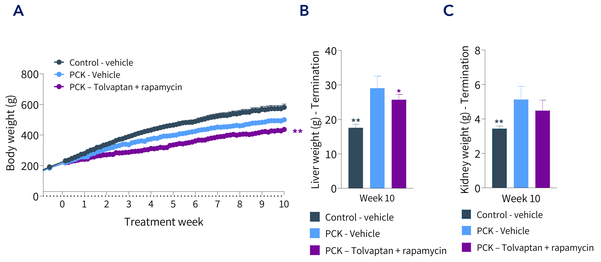


Figure 2. Body weight, kidney and liver weight. (A) Body weight. **(B)** Liver weight **(C)** Kidney weight. Dunnett's test one-factor linear model. **p<0.01, ***p<0.001 compared to the PCK Vehicle group.

3 Tolvaptan + rapamycin improves albuminuria

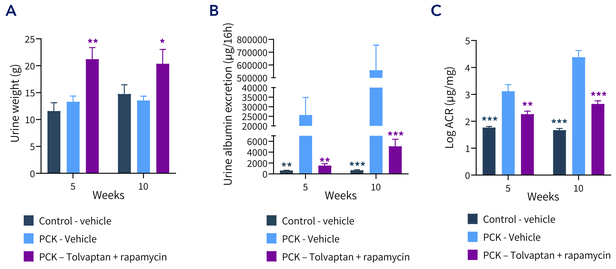
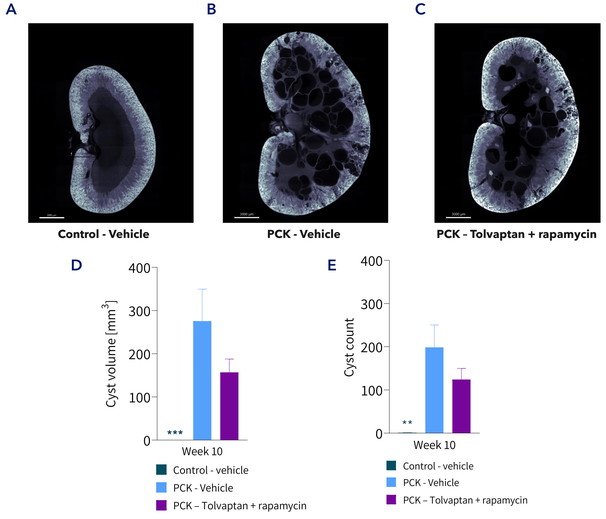


Figure 3. Tolvaptan + Rapamycin treatment improves albuminuria in the PCK rat. (A) Urine weight. **(B)** Urine albumin excretion rate (1h hrs). **(C)** Log uACR. Data is presented as Mean + SEM. Dunnett's test one-factor linear model. *p<0.05, **p<0.01, ***p<0.001 compared to the PCK Vehicle group.

4 Tolvaptan + rapamycin reduces renal cyst formation



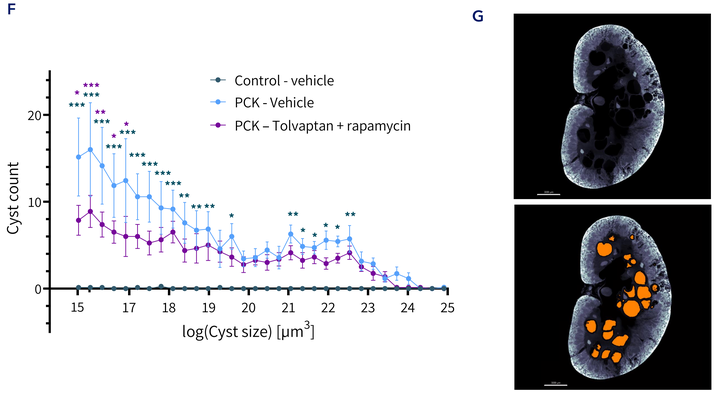


Figure 4. Tolvaptan + Rapamycin reduces renal cyst burden in the PCK rat. Quantitative 3D whole-kidney imaging analysis of **(A)** Control - Vehicle **(B)** PCK – Vehicle **(C)** PCK – Tolvaptan + Rapamycin. **(D)** Cyst volume. **(E)** Cyst count. **(F)** Cyst count vs. cyst size profile. **(G)** Representative 3D whole-kidney image showing automated cyst annotation. *p<0.05, **p<0.01, ***p<0.001 compared to PCK Vehicle group.

Conclusion

Combined Tolvaptan and rapamycin treatment improves albuminuria and reduces cystogenesis in the PCK rat. These findings support nephroprotective effects of this drug combination in PKD and highlights the applicability of the PCK rat in preclinical drug development.

Scan the QR code to learn more about our services within kidney diseases