CFTR Based Therapy for Autosomal Recessive Polycystic Kidney Disease.

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Introduction: ARPKD is associated with systemic and portal hypertension, fibrosis of the liver and kidney and enlarged kidneys, with fusiform dilation of the collecting ducts. Although it has been postulated that CFTR plays a role in fluid secretion in ADPKD, the opposite is true in ARPKD. For example, a double mutant of CFTR and polycystin/polyductin mice develop massively enlarged kidneys and die from renal failure at ~24 days after birth. Thus, knocking down CFTR makes the disease worse.

Methods: We conducted experiments in *pkhd1*$^{del3\text{-}4/del3\text{-}4}$ mouse model of the disease and cholangiocyte cultures from *pkhd1*$^{del/4/del4}$ mice. We injected mice with 30 mg/kg of VX-809 every other day for 30 days and 5 months beginning at 5 days old and necropsied them at 35 and 160 days. The third group we started the treatment at 4 months: treated for 30 days and sacrificed at 155 days. Cultured cholangiocytes were treated with VX-809 (10 μM). In addition, we treated 1 month old mice with one dose of AAV1del27-264CFTR or with AAV1GFP for 60 days and mice were sacrificed at 90 days.

Results: The del3-4 mice developed biliary cysts by 35 days old. The biliary cysts were reduced significantly by the CFTR corrector (VX809) after 1 month or 4 months treatment. The mice treated with one dose of AAV1del27-264CFTR after 2 months showed 80% reduction in biliary cysts.

Conclusion: VX-809 reduces proliferation and the presence of CFTR at the apical membrane while increasing CFTR at the basolateral membrane. Demonstration of liver cyst reduction increases the therapeutic potential of VX-809 as a treatment of ARPKD. The treatment with AAV1 truncated form of CFTR demonstrated a direct link to the role of CFTR in ARPKD and liver cyst reduction increases the therapeutic potential of gene therapy in ARPKD.

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