Chapter 13

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE TREATMENT

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Autosomal dominant polycystic kidney disease results from single gene defect and is the most common inherited disease of kidneys. Félix Lejars firstly used the term polycystic kidney in 1888 although first description of disease was seen at the 16th century after the death of a Poland king. (Balat, 2016). . Nearly 13 million people worldwide are affected from ADPKD with an incidence ranging from 1/400 to 1/1000 live births(Torres & Harris, 2009). It is one of the leading causes of end stage renal disease overall and . approximately 3% of the new dialysis patients annually in the United states("Chapter 1: Incidence, Prevalence, Patient Characteristics, and Treatment Modalities," 2018). Two genetic mutations have been identified until now. PKD-1, encodes polycystin-1, o chromosome 16 and PKD-2, encodes polycystin-2, on chromosome 4. Approximately, 85% of patients with ADPKD HAS pkd-1 mutations and 15% of patients have pkd-2 mutations. Patients with pkd-2 mutations have milder disease course and present with symptoms at an older age compared with patients with pkd-1 mutations (Hateboer et al., 1999). ADPKD is a multisystem disorder with renal and extrarenal manifestations. it is a progressive disease with gradual formation and enlargement of bilateral kidney cysts eventually led to bilateral massive enlargement of kidneys and end stage renal disease. (Oberdhan et al., 2018). In the course of disease, hypertension, pain, hematuria, proteinuria and decreased glomerular filtration rate, cyst hemorrhage, cyst infection, nephrolithiasis are the kidney manifestations which the patients can encounter. Extrarenal manifestations such as hepatic cysts, intracranial aneurysms, mitral valve prolapse, colonic diverticula and arachnoid membrane cysts can also be seen (Luciano & Dahl, 2014). Basic diagnostic method and typical finding of ADPKD are imaging of the kidneys and large kidneys with multiple bilateral cysts respectively although genetic testing may be required very few equivocal cases (Pei & Watnick, 2010). Until recently, the only treatment options for ADPKD is the treatment of cyst related complications and nonspecific measures slowing down the progression to ESRD as a low salt diet, dietary protein restriction and strict blood pressure control. Recent

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Tolvaptan Safety and Efficacy in ADPKD (REPRISE) study was designated to evaluate the efficacy and safety of tolvaptan in patients with more advanced disease (lower GFR levels) than TEMPO study. The study showed that tolvaptan slowed down GFR decline in advanced stage ADPKD patients compared with placebo (Torres, Chapman, et al., 2017). As result of these studies, tolvaptan has been approved for the treatment of ADPKD in some guidelines and recently it was approved by the US Food and Drug Administration (FDA) for the use in ADPKD patients who are at risk for rapid disease progression. In a retrospective study which compared ADPKD patients with kidney transplantation according to treatment with mammalian target of rapamycin (mTOR) inhibitor or the other agents. It showed that native kidney volume decreased with the usage mTOR inhibitor (Qian et al., 2008). In a double blind study, everolimus was compared with placebo. The study showed that everolimus slowed down the increase in kidney volume but it did not prevent the progression of renal impairment (Walz et al., 2010). In an 18 month randomized controlled trial, it was shown that sirolimus did not prevent kidney growth (Serra et al., 2010). Based on the knowledge in the literature, mTOR inhibitorS are not yet suggested for the treatment of ADPKD. In a recent phase-II study, bosutinib was compared with placebo and it was found that bosutinib reduced kidney growth rate (Tesar et al., 2017).there are also ongoing studies with several molecules to target disease progression.

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