THE CURRENT STATUS OF DRUG DEVELOPMENT TO TREAT POLYCYSTIC KIDNEY DISEASE IN THE UNITED STATES

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Polycystic kidney disease (PKD) is an inherited disorder in which clusters of cysts develop predominantly in the kidneys. Cysts are noncancerous round sacs containing water-like fluid, that vary in size based on how much fluid is accumulated over time.
Abnormal genes cause polycystic kidney disease. These genetic defects are passed down from generation to generation in one’s family. It is extremely rare for a genetic mutation to be the cause of a person having polycystic kidney disease.
Autosomal dominant polycystic kidney disease (ADPKD)

- Only one parent needs to have the disease in order for it to pass along to the children. If one parent has ADPKD, each child has a 50 percent chance of getting the disease.
- Occurs in 1:1,000 people worldwide, which accounts for 90% of polycystic disease cases.

Autosomal recessive polycystic kidney disease (ARPKD)

- Both parents must have the abnormal genes to pass on this form of the disease. If both parents carry a gene for this disorder, each child has a 25 percent chance of getting the disease.
- This type of PKD occurs in 1:20,000 people worldwide and is less common than ADPKD.
  The signs and symptoms of the disease often appear shortly after birth, but can sometimes appear in the later childhood and adolescent years.
**COMPLICATIONS OF ADPKD**

- **Elevated blood pressure**, which can damage your kidneys and increase your risk of heart disease and stroke.

- **Kidney failure.** Loss of kidney function, due to numerous cysts that develop on the kidneys. The destruction of the kidneys can lead to waste being built up to toxic levels which will cause a condition called uremia.

- **Growth of cysts in the liver.**

- **Growth of an aneurysm** in the brain. A balloon-like bulge in a blood vessel (aneurysm) in your brain can cause bleeding (hemorrhage) if it ruptures.

- **Heart valve abnormalities**, which causes the heart valve to no longer close properly, allowing blood to leak backward.

- **Chronic pain**, which often occurs in the individual’s side or back. This pain can be in relation to urinary tract infection or the development of kidney stones.
DRUGS TO TREAT ADPKD

- There are currently no treatments to address the primary cause of ADPKD. However, preclinical studies indicate that vasopressin V2-receptor antagonists inhibit cyst growth and slow the decline of kidney function.
Drugs are classified by the way they function to treat particular conditions and the chemical properties of the active ingredient in them.

Vasopressin antagonists are drugs that bind to vasopressin receptors such as (V2) and block the action of vasopressin (antidiuretic hormone, ADH), which is a hormone released by the pituitary gland. Vasopressin causes vasoconstriction and increases reabsorption of water by the kidneys. Vasoconstriction is the contraction of blood vessels, which increases blood pressure.
Vasopressin

Vasopressin type 2 receptor antagonist

V2 receptor

Aquaporin-2

Increase in water permeability

- Concentrated urine
- Decreased free water clearance
- Lowering of serum sodium

- Dilute urine
- Increased free water clearance
- Raising of serum sodium

Source: Kidney Int © 2012 International Society of Nephrology
Tolvaptan is a V2-receptor antagonist. It blocks the action of vasopressin, which causes high blood pressure and the reabsorption of water by the kidneys.
CLINICAL TRAIL OF TOLVAPTAN DRUG ON ADPKD PATIENTS

- **Method:** Otsuka Pharmaceuticals funded a 3-year, phase 3 trial (2007-2009)
  - 1,445 ADPKD patients, age 18-50
  - Multicenter, double-blind, placebo-controlled
  - Tolvaptan dosing was started in daily morning and afternoon doses, with weekly increases according to patient-reported tolerability. For 3 years patients took the highest dose that they reported as tolerable.

- **Results:** Over a 3 year period:
  - Per-year increase in total kidney volume was 2.8% in the tolvaptan group versus 5.5% in the placebo group
  - End point favored tolvaptan over placebo, with lower rates of worsening kidney function.
  - Administration of tolvaptan for 36 months was associated with slowed kidney growth and functional decline and with a reduced frequency of ADPKD-related complications among patients with a large kidney volume.

- **Conclusion:** Tolvaptan, as compared with the placebo, slowed the increase in total kidney volume and the decline in kidney function over a 3 year period in patients with ADPKD, but was associated with a higher discontinuation rate, due to adverse events such as drug-induced liver injury, skin neoplasms, glaucoma, hypernatremia, increased sodium levels, increased uric acid, gout, and dehydration.
"The FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation."

The advisory committee to the US Food and Drug Administration (FDA) voted 9 to 6 not to recommend the tolvaptan drug for the treatment of ADPKD.

During the FDA advisory meeting, Dr. Linda F. Fried, chief of peritoneal dialysis at Veterans Affairs Pittsburgh Healthcare System, stated: "I think the evidence is promising, but on balance, the risk–benefit ratio wasn't there. For a medication that's going to need to be taken lifelong, you don't have long enough follow-up data in the early disease or good data in later disease,"

The cost of renal replacement therapy for ADPKD alone exceeds 1 billion dollars annually
The goal of the European Commission's health and food safety department is to “make Europe a healthier, safer place, where citizens can be confident that their interests are protected. A zero-risk society may not be possible but we are doing as much as we can to reduce and manage risks for our citizens.”

The European Commission has granted marketing authorization for the tolvaptan drug to be used for the treatment of ADPKD.

The marketing authorization for tolvaptan is based on the findings of the Otsuka Pharmaceuticals funded clinical trial.

In support of the tolvaptan drug being used in Europe, Professor Ron T. Gansevoort, from the University Medical Centre Groningen, an expert in the field of polycystic kidney disease stated that: “Until now, healthcare professionals have focused on treating the signs and symptoms of ADPKD, with no specific treatment available to treat the disease. Tolvaptan represents a significant medical breakthrough in the management of ADPKD. For the first time, healthcare professionals can modify the progression of the disease and preserve kidney function, with the potential to improve patients’ quality of life and long-term outcomes.”

Tolvaptan was first approved for patients with ADPKD in Japan in March 2014 and was approved for ADPKD in Canada in February 2015.
The treatment of individuals with ADPKD involves discipline in diet, fluid intake, and blood pressure control. The individual must also avoid harmful drug intake and other negative lifestyle choices. The application of these positive practices early in the development of the disease should decrease the progress of kidney size and preserve proper kidney function to a degree. Effective treatment also requires a collaborative effort from the specialists and the patient to work together in following through with positive practices that will make a difference in the progression of ADPKD.
To conclude, polycystic kidney disease is extremely damaging to ones overall physical health and well-being. Since the disease is genetically inherited and there is no cure, many individuals feel hopeless in their struggle with the complications of the disease. Therapeutic measures only work to an extent, and drugs such as tolvaptan cause many adverse effects that diminish the effectiveness of the positive outcomes. However, there is hope for individuals suffering from ADPKD. Through extensive scientific research and social awareness, positive progress can be made. In June 2015 researchers from the University of California Santa Barbara found a way to reach the growth factors that promote cyst growth in polycystic kidney disease. They suggest it opens the possibility for repurposing a large number of existing drugs to treat the genetic disorder. With further research, clinical trials and technological innovation, the future is bright!


