# Post-transplant drug may also help patients with common genetic kidney disease

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The immunosuppressive drug sirolimus considerably improves the kidney health of patients with autosomal dominant polycystic kidney disease (ADPKD), according to a study appearing in an upcoming issue of the *Journal of the American Society Nephrology* (JASN). The results suggest that this agent may be a promising treatment option for patients with ADPKD—the most common genetic kidney disease and a major cause of kidney failure.

ADPKD causes cysts to grow within the kidney, affecting nearly 600,000 Americans and more than 10 million people worldwide. With no effective treatment, the disease often leads to enlarged kidneys and eventually kidney failure.

Research reveals that certain signals within cells may contribute to cyst growth in patients with ADPKD. These signals are part of what is known as the mammalian target of rapamycin (mTOR) pathway that controls cell growth and division. Giuseppe Remuzzi, MD, FRCP (Mario Negri Institute for Pharmacological Research, Bergamo, Italy) and his colleagues investigated, in a small pilot study, whether blocking this pathway with the mTOR inhibitor sirolimus (originally called rapamycin) might be an effective treatment strategy against ADPKD. (Sirolimus also acts as an immunosuppressant and is currently used to prevent rejection of kidney transplants.) Their clinical trial, called SIrolimus Treatment in Patients with Autosomal Dominant Polycystic Kidney Disease: RENAl Efficacy and Safety (SIRENA), examined how six months of treatment with sirolimus or conventional therapy affected different measures of kidney volume in 21 patients with ADPKD who had normal or slightly impaired kidney function.

Six of the 21 patients withdrew from the trial prematurely for various reasons. Data from the remaining patients demonstrated that sirolimus had a beneficial effect on the kidneys. Sirolimus therapy halted the growth of kidney cysts and increased the volume of healthy essential kidney structures, with an overall trend to slow the increase of total kidney volume. The investigators suspect that sirolimus may allow healthy kidney tissue to expand by relieving it from the compressing effects of surrounding cysts.

None of the patients in this trial developed serious side effects from receiving sirolimus. "This is the first randomized clinical study with mTOR inhibitor in ADPKD patients whose results have become available, and the findings provide the rationale for additional clinical trials aimed to assess whether chronic sirolimus therapy may improve clinical outcomes of ADPKD patients in the long run," said Dr. Remuzzi.

Study co-authors include Norberto Perico, MD, Luca Antiga, PhD, Anna Caroli, Nadia Rubis, Olimpia Diadei, Giulia Gherardi, Silvia Prandini, Andrea Panozo, MD, Rodolfo Flores Bravo, MD, Sergio Carminati, Felipe Rodriguez De Leon, MD, Flavio Gaspari, Monica Cortinovis, Nicola Motterlini, Bogdan Ene-Iordache (Mario Negri Institute for Pharmacological Research, in Bergamo, Italy); Piero Ruggenenti, MD (Mario Negri Institute for Pharmacological Research and Azienda Ospedaliera Ospedali Riuniti Bergamo); Giorgio Fasolini, MD, Mariateresa Cafaro, MD, Patrizia Ondei, MD (Azienda Ospedaliera Ospedali Riuniti Bergamo); and Andrea Remuzzi (Mario Negri Institute for Pharmacological Research and the University of Bergamo).

In reviewing the results of Dr. Remuzzi's study in an accompanying editorial, Robert Schrier, MD (University of Colorado Denver) stated that they give hope for the treatment of patients with ADPKD. He noted, however, that six months of sirolimus treatment was associated with mildly abnormal liver function tests, as well as increased cholesterol, decreased red blood cells, and increased protein excretion in the urine. "This is potentially bothersome regarding possible lifelong therapy for ADPKD," he wrote. "Thus, results of larger and longer follow-up studies in ADPKD patients with mTOR inhibitors will be very important."

**More information:** The article, entitled "Sirolimus Therapy to Halt the Progression of ADPKD," (doi 10.1681/ASN.2009121302) will appear online on May 13, 2010. The accompanying editorial "Randomized Intervention Studies in Human Polycystic Kidney and Liver Disease," (doi 10.1681/ASN.2010030262) was published online on April 29, 2010.

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