Drug Effective in Treating Kidney Disease in Diabetic Patients

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Researchers at the University of California, San Diego School of Medicine, the National Institutes of Health (NIH) and the Mayo Clinic have published promising results of a clinical study using an experimental anti-fibrotic and anti-inflammatory drug called pirfenidone to treat patients with diabetic nephropathy. Their study will be published in the April 21 issue of the *Journal of the American Society of Nephrology* (JASN).

Diabetic nephropathy remains the leading cause of end-stage kidney disease (ESKD) in the United States. It is a common complication of diabetes, in which kidney cells are damaged as a result of high blood sugar levels.

"The dramatic finding of this exploratory study is that an appropriate dose of pirfenidone not only halted decline but actually improved kidney function in these patients," said Kumar Sharma, MD, FAHA, professor of medicine in the UCSD division of nephrology and director of the Center for Renal Translational Medicine, who headed the study.

The principal process underlying the progression of chronic kidney disease to ESKD – where dialysis is required to keep a patient alive – is called renal (kidney) fibrosis. The fibrosis, or scarring, damages tiny blood vessels in the glomerulus, structures that filter and remove waste from the blood, and in between tubular cells.

Transforming growth factor beta (TGF-β) is a protein that controls many cellular functions, including extracellular matrix accumulation. TGF-β is stimulated in the diabetic kidney due to uncontrolled blood sugar and elevated blood pressure and can promote renal fibrosis.

"To date, therapies for diabetic nephropathy have been limited to drugs that improve blood pressure or control blood sugar levels," said Sharma. Instead, pirfenidone seems to work by blocking TGF-β; in effect, shutting down the growth factors that cause renal fibrosis.

The UCSD researchers previously observed a very dramatic benefit in a mouse model of diabetic kidney disease, in a study published in JASN two years ago. The animal studies showed improvement in matrix accumulation at gene and protein levels with just four weeks of treatment.

The new randomized, double-blind study of 77 patients with diabetic nephropathy was conducted at Thomas Jefferson Hospital in Philadelphia, the Mayo Clinic in Rochester and the NIH, and comprised three study groups: one group received a high dose of pirfenidone (2400 mg); one group received a low dose of pirfenidone (1200 mg); and a control group.

The UCSD researchers analyzed the rate of decline in kidney function in the three groups by measuring the estimated glomerular filtration rate, or eGFR. They found a significant improvement in the low-dose group over the course of the one-year study. There was no seeming benefit to those patients who received the high dose, suggesting that higher doses may not be tolerable in the diabetic population with moderate to advanced chronic kidney disease.

Sharma states the next step is to perform a larger clinical study and to identify personalized biomarkers, to determine which patients are most apt to show improvement on the drug. "This drug might also be useful in treating other types of fibrotic disease," he added.

"We have previously found that pirfenidone slows progressive loss of kidney function in another chronic kidney disease, called focal segmental glomerulosclerosis," said Jeffrey B. Kopp, MD, NIH/NIDDK intramural researcher and Capt., USPHS. "By extending these findings to the most common chronic kidney disease – diabetic kidney disease – the present study suggests that pirfenidone may have broad utility to help patients maintain kidney function longer."

Additional contributors to the study included Joachim H. Ix, Anna V. Mathew, Shoba Sharma, Michael Donohue, Satish RamachandraRao, and Ronghui Xu, of UCSD; Monique Cho and Jeffrey B. Kopp, National Institute of Diabetes and Digestive and Kidney Diseases, NIH; Axel Pflueger and Fernando C. Fervenza, Mayo Clinic, Rochester, Minnesota; Tracy A. McGowan, formerly at Thomas Jefferson University and now at Johnson and Johnson; Stephen R. Dunn, Kimmel Cancer Center and Thomas Jefferson University; Bonita Falkner and Barbara Francos, Thomas Jefferson University.

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