Combination therapy stops loss of kidney function in rare genetic disease

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A combination of two types of blood pressure-lowering drugs—an angiotensin-converting enzyme inhibitor (ACEI) plus an angiotensin-receptor blocker (ARB), added to enzyme replacement therapy (ERT) with agalsidase-beta (Fabrazyme®, Genzyme Corporation, Cambridge, MA)—is the first treatment shown to stop progressive loss of kidney function in patients with severe kidney involvement due to the rare genetic disorder Fabry disease, reports a study in the September Journal of the American Society of Nephrology.

"While Fabry disease is very rare, our study shows that controlling urine protein excretion will slow progression of kidney disease, even though the achieved blood pressures were lower than are usually targeted in treating chronic kidney disease," says Dr. David Warnock of University of Alabama, Birmingham, one of the study authors.

Dr. Warnock and colleagues report encouraging results with ACEI/ARB therapy in eleven patients with progressive loss of kidney function related to Fabry disease (Fabry nephropathy). Fabry disease is a rare genetic disorder caused by problems with an enzyme called alpha-galactosidase-A, which the body needs to metabolize lipids (fatty substances). Even with treatment to replace the missing enzyme, buildup of lipids can cause progressive kidney, brain, and heart disease. In the current study, four patients had relatively mild kidney disease (stage 1 to 2), while seven had more severe loss of kidney function (stage 3 to 4).

All patients received ERT and combined ACEI/ARB treatment. The

ACEIs and ARBs are widely used in patients with chronic kidney disease and proteinuria—"leakage" of protein into the urine associated with progressive loss of kidney function. Treatment is usually based on the patient's blood pressure. However, the situation is different in patients with Fabry disease, who often have low to normal blood pressure despite kidney disease.

The ACEI/ARB combination effectively controlled the patients' level of proteinuria. Among six patients with severe kidney disease, treatment greatly slowed the rate of deterioration in kidney function and reduced urine protein loss—in contrast, previous studies have reported no beneficial effect of ERT alone on proteinuria. After an average of two and a half years' treatment, the UAB patients had only a minimal decline in kidney function, which was not significantly from zero.

The combination of ERT and ACEI/ARB therapy also stabilized kidney function in patients with less severe kidney disease and milder degrees of proteinuria. Aside from some minor problems related to episodes of low blood pressure, there were no serious side effects of ACEI/ARB treatment.

Studies in other groups of patients with chronic kidney disease have highlighted the importance of treatment with an ACEI and/or ARB to control proteinuria. Although most of the improvement probably results from reductions in blood pressure, other effects may contribute as well. In patients with Fabry disease, ERT is of some help in treating mild kidney disease, but is less effective in those with more severe kidney disease and proteinuria.

"This work shows for the first time that it is possible to stop progressive decline of kidney function in patients who have Fabry disease with advanced kidney involvement and proteinuria," Dr. Warnock concludes. "The results were everything we hoped for, and are now being confirmed

in a sixteen-site international multicenter trial."

Source: American Society of Nephrology