Atrasentan with Current Optimal Therapy Reduces Albuminuria in Type 2 Nephropathy

Atrasentan, an oral endothelin receptor antagonist, reduces albuminuria and improves the lipid profile in patients with diabetic nephropathy when given with optimal therapy using an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), a recent study shows.

"It has a nearly 40 percent reduction of albuminuria over the full 12-week stretch [of the trial], with minimal side effects," Dick de Zeeuw, MD, PhD, professor and chair of the department of clinical pharmacology at University Medical Center Groningen in The Netherlands, reported at the 50th Congress of the European Renal Association—European Dialysis and Transplant Association in Istanbul. Besides being a marker of kidney damage, albuminuria is also a promoter of kidney damage and a cardiovascular risk factor, possibly because it indicates generalized vascular and endothelial dysfunction.

Atrasentan is an investigational compound that blocks the effect of endothelin-1 at the endothelin-A receptor. Endothelin-1 is a peptide that constricts blood vessels in the kidney and has a negative effect on kidney function.

Although optimal therapy with compounds that target the renin-angiotensin-aldosterone system, such as ACE inhibitors and ARBs, help protect the kidneys and reduce albuminuria, some risk persists. "There is a pressing need for new medications to treat nephropathy in patients with type 2 diabetes who have a high risk to end up in dialysis," de Zeeuw said.

He presented the results of two parallel, double blind, placebo-controlled, multinational phase 2b studies (total n = 211) in which patients with type 2 diabetes and nephropathy received maximum tolerated labeled doses of ACE inhibitors or ARBs. They also received atrasentan at 0.75 mg/day (n = 78), 1.25 mg/day (n = 83), or placebo (n = 50) to evaluate the efficacy of the compound in lowering albuminuria and its safety. At baseline, patients in the three groups all had macroalbuminuria, as determined by the urinary albumin-to-creatinine ratio (878 mg/g, 826 mg/g, and 671 mg/g, respectively).

At the end of the 12-week trials, patients experienced sustained reductions in the primary endpoint of the urinary albumin-to-creatinine ratio: a 36 percent geometric mean decrease in the group receiving the 0.75-mg dose and a 44 percent decrease at the 1.25-mg dose versus a 2 percent increase in the placebo group (both $p < 0.001$ vs. placebo). Just over half of the patients in each group experienced a decrease of more than 30 percent in urinary albumin-to-creatinine ratio. Significant decreases ($p < 0.001$) were evident as early as 2 weeks for the atrasentan groups. There were also decreases in low-density lipoprotein cholesterol and triglyceride levels in the active drug groups.

Adverse events similar to placebo

The rates of adverse events were similar among the three groups. Peripheral edema occurred in 35 percent of patients in the 0.75-mg group and in 42 percent in the 1.25-mg and placebo groups. Diarrhea and constipation occurred in 13, 21, and 14 percent of the people in the three arms, respectively. Adverse events caused 8 percent of participants to drop out of the low-dose group and 15 percent to discontinue the study in the high-dose group. Edema was the most common reason for participants to discontinue the study. None discontinued in the placebo group.

Estimated GFRs dropped by less than 1 mL/min per 1.73 m^2 in both of the atrasentan groups, but these changes were no different from those in the placebo group ($p = 0.412$ and $p = 0.355$ for the 0.75-mg and 1.25-mg doses, respectively).

A phase 3 randomized, double-blind, placebo-controlled trial is planned using the 0.75-mg daily dose of atrasentan, which was determined in the phase 2b trials to have the best balance of efficacy and safety. The trial will investigate renal as well as cardiovascular outcomes when atrasentan is given on top of current optimal standard of care to patients with type 2 diabetic nephropathy. It is planned to involve more than 4000 patients and to run for 4 years.

As noted by de Zeeuw, other endothelin antagonists have been tested in type 2 diabetes and have lowered albuminuria. A trial of avosentan was stopped early because of fluid retention leading to congestive heart failure. He said that this adverse effect was blamed on the high dose of the drug, and current trials are looking at a lower dose that might retain the albumin-lowering effects but avoid fluid retention.

Mediterranean Diet Linked to Lower Mortality in Older Men with Chronic Kidney Disease

For people with chronic kidney disease (CKD) who followed a Mediterranean-style diet, renal function improved. The more these people adhered to such a diet, the more improvement was seen in survival, according to the results of a study presented at the 50th Congress of the European Renal Association—European Dialysis and Transplant Association in Istanbul, Turkey, in May.

The Mediterranean diet consists largely of plant-based foods such as fruits and vegetables, whole grains, legumes, and nuts; healthful oils such as olive and canola; and some fish and poultry but limits red meat and saturated fats. Red wine in moderation is optional; it has been associated in various populations with lower risks of illness and mortality. However, few data exist regarding kidney function in community-dwelling adults who follow such a diet.

Juan Carrero, PhD, of the Karolinska Institute in Stockholm and co-workers conducted an observational study on a population-based cohort (the Uppsala Longitudinal Study of Adult Men) of 1110 Swedish men around 70 years old to see whether the men who followed a Mediterranean diet had improved kidney function, lower cardiometabolic risks, and reduced mortality. From 7-day diet diaries that the men recorded, the researchers determined their dietary habits, from which they calculated a Mediterranean Diet Score, allowing classification of the participants as low, medium, or high adherents to such a diet.

Within the cohort, 506 men had GFRs of less than 60 mL/min per 1.73 m^2 and were therefore considered to have CKD. Deaths were recorded during a median follow-up time of 9.9 years.

During follow-up, 168 of the 506 individuals with CKD died. Better adherence to the diet was independently associated with better survival. For every two-point increase in the Mediterranean Diet Score, the investigators observed an 18 percent lower risk of death, with a stronger association in those individuals who had adequate dietary intakes.

Of the individuals who died, the adherence groups did not differ in their cardiometabolic risk factors. "Most potential explanatory risk factors for the mortality association, such as obesity, blood pressure, lipoproteins, glucose, insulin, or inflammation, did not associate with a greater or poorer adherence to the diet," Carrero said. To some extent, this lack of association with such risk factors may be attributable to the homogeneous nature of the cohort: men of about the same age, from the same region, and of the same ethnicity. "In addition…the benefits of the Mediterranean diet may be mainly accounted for by individual nutrients, such as high fiber intake and high PUFA [polyunsaturated fatty acids] but low SFA [saturated fatty acid] intake rather than by the score as a whole," he said.

In comparison with low adherents to the diet, high adherents had a 42 percent lower risk of CKD after adjustment for body mass index, physical activity, smoking, education, hypertension, hyperlipidemia, and diabetes (adjusted odds ratio 0.58; 95 percent confidence