Findings
European Renal Association—European Dialysis and Transplant Association Congress

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 m² 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; healthy 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 may be mainly accounted for by individual nutrients, such as polyunsaturated fatty acids but low SFA [saturated fatty acid] intake rather than by the score as a whole,” he said.

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 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
Cardiovascular Risk Profile Improves with Sevelamer Use in Diabetic Nephropathy

Markers of cardiovascular protection rose when diabetic patients with chronic kidney disease were treated with the phosphate binder sevelamer carbonate (sevelamer). In a randomized trial comparing sevelamer with the phosphate binder calcium carbonate, the group receiving sevelamer experienced increased levels of estrogen receptor-α (ER-α), two markers of antioxidant activity, and defenses against advanced glycation end products.

Phosphate is a component of diet and is absorbed in the small intestine. The kidneys excrete excess phosphate, but in the case of impaired renal function, they cannot maintain proper phosphate balance. Studies have shown that the resulting hyperphosphatemia correlates with increased mortality. Dietary restriction of phosphate intake and the use of oral phosphate binders can help control phosphate balance.

Sevelamer is a non-calcium-containing phosphate binder that may also have additional beneficial effects on other factors that promote cardiovascular disease, a major cause of mortality in chronic kidney disease.

Oxidative stress and inflammation are part of the process of cardiovascular disease. ER-α is known to reduce these factors in men and women, but ER-α activity is reduced in diabetic kidney disease, suggesting that decreased ER-α may contribute to the increased risk and prevalence of cardiovascular disease in this population. Simply put, less ER-α leads to more oxidative stress and inflammation, leading to more cardiovascular damage. In addition, advanced glycation end products, the result of hyperglycemia in diabetes, elevate the levels of oxidative stress and inflammation.

Besides binding phosphate, sevelamer is also thought to block the absorption of advanced glycation end products from food, further helping to limit oxidative stress and inflammation. Given that sevelamer does not contain calcium, it may also lower the progression of vascular calcification in comparison with calcium-containing phosphate binders.

Testing effect of sevelamer on cardiovascular risk factors

To test the hypothesis that sevelamer restores the levels of ER-α and has beneficial effects on other risk factors, Gary Striker, MD, research professor of geriatrics and medicine at the Mount Sinai School of Medicine in New York City, and colleagues compared the effects of sevelamer and calcium carbonate on the levels of ER-α and other markers of antioxidant and anti-advanced glycation end products in peripheral blood mononuclear cells (white blood cells). They presented their findings at the 50th Congress of the European Renal Association—European Dialysis and Transplant Association.

The trial randomly assigned men and women with type 2 diabetes to sevelamer 4800 mg/day (n = 56) or to calcium carbonate 1590 mg/day (n = 50) for 6 months. The inclusion criteria were hemoglobin A1c level greater than 6.5 percent, an estimated GFR of 25–80 mL/min per 1.73 m², and albumin excretion greater than 300 mg/day. The mean ages of the men and women in the sevelamer and calcium carbonate groups ranged from 60.1 to 67.5 years.

In an analysis at 3 months assessing the amount of change from baseline in the biomarkers, the group as a whole (both men and women analyzed together) showed a marked increase in ER-α if they received sevelamer as opposed to calcium carbonate (p = 0.003). There were also significant increases in two biomarkers of antioxidant effects, Nrf2 and advanced glycated end-product receptor 1 (AGER1) (p = 0.009, p = 0.028, respectively). Nrf1 activates multiple pathways within cells to protect against oxidative stress and inflammation, and AGER1 suppresses oxidative stress caused by cellular oxidants.

The levels of two inflammatory markers predictive of cardiovascular disease and progression of diabetic kidney disease (tumor necrosis factor receptor 1 and RAGE) decreased in the group receiving sevelamer.

There were differences between men and women in some of the various markers when the sexes were analyzed separately, but the major finding of increased levels of ER-α was consistent regardless of sex.

The investigators concluded that sevelamer carbonate restored levels of ER-α in both men and women and that this effect was associated with a reduction in markers of oxidative stress, inflammation, progression of diabetic kidney disease, and risk factors for cardiovascular disease, as well as improvements in antioxidant defenses.

It is important to note that the study involved surrogate markers that indicate risk. It did not directly investigate clinical outcomes such as cardiovascular events or progression of kidney disease. Larger trials of longer duration are planned to see whether the findings in this trial will be reflected in a reduction in clinical events.

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