Bardoxolone Upped eGFR in Diabetic CKD

BY M. ALEXANDER OTTO

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF NEPHROLOGY

A 24-week course of bardoxolone methyl, an experimental antioxidant inflammation modulator, improved estimated glomerular filtration rates in chronic kidney disease patients with type 2 diabetes, according to a randomized phase IIb study funded by Reata Pharmaceuticals Inc.

A phase III study slated to start next year will test whether the mean eGFR improvement of 10.1 mL/minute per 1.73 m^2 leads to better patient outcomes, according to nephrologist Pablo Pergola of the University of Texas Health Science Center, San Antonio.

VITALS

Major Finding: Bardoxolone methyl improved eGFR in diabetic CKD patients by a mean of 10.1 mL/minute per 1.73 m^2.

Data Source: Phase IIb randomized, double-blind, placebo-controlled trial enrolling 227 patients.

Disclosures: The study was funded by the drug's sponsor, Reata Pharmaceuticals. The lead investigator said he had no conflicts of interest.

"You want to make sure this drug will be associated with a clinical outcome," said Dr. Pergola, the lead investigator of the phase IIb study.

Patients in the randomized, double-blind, placebo-controlled trial were assigned to 25-mg, 75-mg, or 150-mg daily doses of bardoxolone or to placebo. Each group had 57 subjects, except the 150-mg group, which had 56.

In addition to type 2 diabetes, subjects had stage 3b or 4 chronic kidney disease (CKD), with an eGFR of 20-45 mL/min per 1.73m^2.

Their median age was 67 years, and all were on standard-of-care therapy – 98% of patients took ACE inhibitors or angiotensin-receptor blockers.

At 24 weeks, bardoxolone patients had a mean eGFR gain of 10.1 mL/minute per 1.73 m^2, with improvements noted in each group ranging from 8.3 to 11.5 mL/minute per 1.73 m^2, a significant difference from the 0.1–mL/minute per 1.73 m^2 gain with placebo.

About 73% (124) of patients in each bardoxolone group had at least a 10% eGFR increase; 25% (43) had more than a 50% increase.

Increased eGFRs also correlated with decreased blood-urea-nitrogen levels, decreased serum phosphorous and uric acid levels, and improved CKD stage.

Adverse events were more common in the bardoxolone groups; 49% reported muscle spasms, compared with 12% in the placebo group. The spasms were thought to be treatment related, as were nausea, hypomagnesemia, and diminished appetite. ■

Intensive Control Curbed Renal Events

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES

STOCKHOLM – An intensive glucose control regimen aiming for a hemoglobin A_{1c} level of 6.5% or lower significantly reduced the incidence of renal events in patients with established type 2 diabetes, according to findings from a large Australian study.

The total number of renal events in 5,571 patients randomized to intensive treatment was reduced by 11% (26.9% vs. 30%), compared with 5,569 patients who followed a standard glucose control regimen, Dr. Sophia Zoungas said at the meeting.

The data come from the glucose-lowering arm of the multination ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) study, which examined the effects of both blood pressure lowering with perindopril/indapamide and glucose-lowering gliclazide MR in a total of 11,140 patients. Primary trial findings were reported in 2007 and 2008 (www.advance-trial.com).

The current analysis evaluated the incidence of renal events at a median follow-up of 5 years, when the mean HbA_{1c} level achieved was 6.5% in the intensive treatment arm and 7.3% in the standard control group, reported Dr.

VITALS

Major Finding: Renal events were reduced by 11% among those randomized to intensive therapy aiming for an HbA_{1c} of less than 6.5%, compared with those receiving standard glucose control.

Data Source: The ADVANCE study, which randomized 11,140 patients with type 2 diabetes.

Disclosures: The study received funding from the National Health and Medical Research Council of Australia and from Servier, the maker of Preterax and Diamicron MR. Dr. Zoungas disclosed that she has received honoraria from Servier.

Zoungas, who is head of the diabetes research program at the George Institute for Global Health, Sydney.

The incidence of new microalbuminuria, defined as a urine albumin-to-creatinine ratio (UACR) of 30-300 g/mg, was reduced by 9% with intensive therapy, occurring in 23.7% of patients in that group compared with 25.7% of the standard treatment group. New-onset macroalbuminuria (UACR greater than 300 g/mg) was reduced by 30% (2.9% vs. 4.1%). New or worsening nephropathy, defined as progression of albuminuria by at least one stage (from normoalbuminuria to either micro- or macroalbuminuria) was 21% lower with intensive therapy (4.1% vs. 5.2%), and end-stage renal disease was reduced by 36% (0.4% vs. 0.6%).

All of the differences were statistically significant except for those involving end-stage renal disease, which nonetheless showed a "small but important trend," said Dr. Zoungas, also of Monash University, Clayton, Australia.

Among 3,261 patients who had albuminuria at baseline, regression by at least one stage occurred in 61.8% of the intensive treatment group, compared with 55.8% of the standard group, for a hazard ratio of 1.15. Regression to normoalbuminuria occurred in 56.8% vs. 49.7%, with a hazard ratio of 1.2. Both were highly statistically significant, she said.

Renal benefit was seen even in those patients who had HbA_{1c} levels less than 7% at baseline. "We could not identify an HbA_{1c} threshold below which renal benefit was lost," Dr. Zoungas said. ■