Olmesartan Delays Microalbuminuria in Type 2

BY MIRIAM E. TUCKER

FROM THE NEW ENGLAND JOURNAL OF MEDICINE

Use of the angiotensin II receptor antagonist olmesartan was associated with a delayed onset of microalbuminuria in a randomized, double-blind controlled trial involving more than 4,000 patients with type 2 diabetes.

The time to onset of microalbuminuria was increased by a significant 23% with olmesartan compared with placebo in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial. But of concern, patients who received olmesartan had a higher rate of fatal cardiovascular events, mostly among patients with preexisting cardiovascular disease, Dr. Hermann Haller and his associates said (N. Engl. J. Med. 2011;364:907-17).

The study randomized 4,449 white patients with type 2 diabetes, aged 18-75 years, to either 40 mg/day of olmesartan or placebo. Additional antihypertensive drugs that do not block the renin-angiotensin system were used as needed to achieve blood pressure of less than 130/80 mm Hg. Nearly 80% of the olmesartan group and about 71% of the placebo group achieved that level of blood pressure control at month 48, said Dr. Haller of Hannover (Germany) Medical School and his ROADMAP trial colleagues.

During a median follow-up of 3.2 years, microalbuminuria developed in 8.2% of the 2,160 patients in the olmesartan group for whom albumin-to-creatinine ratio could be evaluated, compared with 9.8% of the 2,139 evaluable placebo patients. Microalbuminuria was defined as a urinary albumin-to-creatinine ratio of more than 35 in women or more than 25 in men.

The median time to onset of microalbuminuria – the primary study end point – was 576 days in the placebo group and 722 days in the olmesartan group, with a hazard ratio of 0.77. After adjustment for small baseline differences in body mass index, systolic blood pressure, and lipid levels, the hazard ratio remained significant, at 0.75.

The mean estimated glomerular filtration rate – a secondary end point – dropped from 85.0 mL/min per 1.73 m^2 at baseline to 80.1 mL/min per 1.73 m^2 at the last assessment in the olmesartan group, compared with 84.7 to 83.7 mL/min per 1.73 m^2 with placebo, a significant between-group difference in change from baseline. End-stage renal disease did not develop in any patient, and approximately 1% in each group had a doubling of serum creatinine level, Dr. Haller and his associates reported.

The proportion of patients who reached the composite secondary end point of cardiovascular complications or cardiovascular-related death was also similar between the two groups, 4.3% of the olmesartan group and 4.2% of the placebo group. The death rate overall was very low, just 1.2% of the olmesartan patients and 0.7% of those taking placebo.

However, the number of deaths from cardiovascular causes was higher in the olmesartan group, 15 vs. 3 on placebo, primarily because of fatal myocardial infarction (5 vs. 0) and sudden cardiac death (7 vs. 1). The majority of deaths from cardiovascular causes, 12 of 18, occurred in the subgroup of 1,104 patients who had preexisting coronary heart disease. Among patients with preexisting heart disease, there were 11 deaths from cardiovascular causes with olmesartan vs. 1 in the placebo group, giving event rates of 6.9 vs. 0.7/1,000 person-years, the investigators said.

Other adverse event rates were similar between the two groups. Serious adverse events occurred in 15.0% with olmesartan vs. 15.2% with placebo, and drug-related adverse events occurred in 11.4% vs. 7.5%. That difference was mostly due to more episodes of hypotension (58 vs. 6 patients) and dizziness (103 vs. 61 patients) with olmesartan.

This study was funded by Daiichi Sankyo. Dr. Haller reported receiving payment for board membership from Novartis. He said he also receives consulting fees, lecture fees, payment for the development of educational presentations, and/or travel support from Bayer Schering Pharma, Daiichi Sankyo, Roche, Menarini, and Amgen. ■

VIEW ON THE NEWS

FDA Investigates CVD Deaths

Although the analysis is markedly underpowered for cardiovascular end points, given the small number of events in a relatively healthy population of persons with type 2 diabetes, the cardiovascular results of this trial have raised concerns even before publication. While nonfatal cardiovascular events did not differ significantly – 3.6% in the olmesartan group and 4.1% in the controls – fatal cardiovascular events were increased in the olmesartan group, 0.7% vs. 0.1%.

The fact that these signals go in opposite directions, together with the feeling that the study was underpowered to determine cardiovascular risk, suggest to some people that the results may well be due to chance. However, the ROADMAP results, combined with those of ORIENT, have led the FDA to investigate. The excess in cardiovascular mortality in ROADMAP occurred mainly among patients in the lowest quartile of blood pressure, so that may have been a factor.

For now, the FDA's Web site still states that olmesartan's benefits continue to outweigh its potential risks. Some nephrologists and cardiologists agree. Others argue that since there are other angiotensin receptor blockers that can be used to prevent the onset of microalbuminuria that have not shown the same signal, why not prescribe one of those?

JULIE INGELFINGER, M.D., *is deputy editor of the New England Journal of Medicine. She disclosed having received travel/accommodations/meeting expenses from the National Institutes of Health and the Cystinosis Research Foundation. These comments were excerpted from an editorial that accompanied the study (N. Engl. J. Med.2011;384:970-1).*