Olmesartan Lowers Microalbuminuria in Type 2

BY DOUG BRUNK

SAN DIEGO — Olmesartan reduced the risk of microalbuminuria by 23% in normoalbuminuric patients with type 2 diabetes and at least one additional cardiovascular disease risk factor, results from a large European trial showed.

The angiotensin receptor blocker (ARB) also yielded unprecedented blood pressure control for this population.

Those are the first key findings from the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study, presented at the annual meeting of the American Society of Nephrology.

"Despite all of our efforts, we still have problems effectively treating diabetic nephropathy," said the study's steering committee chair, Dr. Hermann G. Haller of the department of nephrology at Hannover (Germany) Medical School. "The problem for prevention is that we have to diagnose and treat it early. Microalbuminuria is the first sign of the pathogenesis of diabetic nephropathy. It is also an important marker of early development of cardiovascular disease and can indicate microvascular disease."

The primary end point of the study was occurrence of microalbuminuria based on two or more positive morning spot urine measurements. Secondary end points were cardiovascular events, renal function, and microvascular morbidity.

With support from Daiichi Sankyo, which markets olmesartan, researchers in 19 countries enrolled 4,449 patients aged 18-75 years with well-controlled type 2 diabetes. All patients were normoalbuminuric (a level of 25 mg/g or less for men, 35 mg/g or less for women) and had at least one additional cardiovascular risk factor such as high triglyceride levels or hypertension. None of the participants had received an ACE inhibitor or an ARB within 6 months of participation.

The patients were randomized to olmesartan 40 mg/day or placebo. The urine albumin creatinine ratio was determined every 6 months. Patients were followed for an average of 3.2 years.

At their discretion, study investigators could add calcium channel blockers, diuretics, or beta-blockers to the regimen to help patients achieve the target blood pressure goal of 130/80 mm Hg.

The patients' mean age was 58 years, mean duration of diabetes was 6 years, mean hemoglobin A_{1c} level was 7.6%, and mean body mass index was 31 kg/m^2. Mean baseline blood pressure was 141/84 mm Hg.

Dr. Haller reported that nearly 80% of patients in the olmesartan group reached the target BP of 130/80 mm Hg at 42 months, compared with 75% of patients in the placebo group. "The percentage of patients reaching the blood pressure goal was very high," he said.

Over the study period, microalbuminuria occurred in 8% of the patients in the olmesartan group and 10% of the patients on placebo, a statistically significant difference. This translated into a risk reduction of 23% for the olmesartan group, compared with the placebo group.

Microalbuminuria is an important marker of diabetic nephropathy, which must be diagnosed and treated early.

DR. HALLER

After 1 year, the first incidence of microalbuminuria occurred in 3% of patients in both groups. For the remainder of the study, fewer patients in the olmesartan group experienced microalbuminuria, compared with the placebo group. "The divergence after 1 year indicates that the specific effects of olmesartan are not due to early hemodynamic changes that would have happened in the first couple of months," Dr. Haller said in an interview. "We think that olmesartan has a specific, perhaps structural effect on the kidney, either in the glomeruli or in the basal membrane, in the microcirculation."

When the researchers assessed the BP effect in the olmesartan group corrected for diastolic and systolic BP, the risk reductions did not reach statistical significance (18% vs. 17%, respectively).

No adverse events from olmesartan were observed on renal outcomes, and the incidence of cardiovascular morbidity and mortality affected fewer than 1% of the entire study population. "Most likely the event rate is very low because of the excellent blood pressure control," Dr. Haller said.

Some cardiovascular events such as a higher incidence of nonfatal stroke and sudden cardiac death were seen in the olmesartan group, compared with the placebo group, but due to the small number of cases, "we have to analyze this further," Dr. Haller emphasized. An observational follow-up study is underway to further understand the long-term benefits of microalbuminuria prevention.

Dr. Haller is a paid consultant for Daiichi Sankyo and several other pharmaceutical companies, and has received honoraria from various drug companies. ■

Predialysis Hemoglobin Low In Diabetic Nephropathy

BY DOUG BRUNK

SAN DIEGO — Patients with diabetic nephropathy have a slightly lower mean level of hemoglobin in the year leading up to the start of renal dialysis, compared with patients who have nondiabetic renal disease, results of a large analysis showed.

The difference persisted after adjustment for several other variables including age, gender, ethnicity, and estimated glomerular filtration rate, Dr. Daniel Ford said in an interview during a poster session at the annual meeting of the American Society of Nephrology.

This reiterates that diabetic nephropathy patients tend to have more anemia than nondiabetic renal patients.

DR. FORD

"This reiterates what we know about patients with diabetic nephropathy—that they do have a tendency to have more anemia than patients with nondiabetic renal diseases," said Dr. Ford, of the United Kingdom Renal Registry, Bristol, England. "I suspect it's because patients with diabetic nephropathy have a higher incidence of concurrent diseases, which would make it more likely that they would suffer with more anemia than patients without diabetic renal diseases."

In what he said is the largest multicenter study of its kind in the United Kingdom, Dr. Ford and his associates evaluated the electronic medical records of 1,823 patients from the U.K. Renal Registry who underwent renal dialysis at seven centers between 2001 and 2006. They extracted data at time points 0, 1, 2, 3, 4, 5, 6, and 12 months prior to the commencement of dialysis and used a quadratic multilevel model to estimate the average pattern of decline in hemoglobin over that period.

The median age of patients was 66 years. Patients with diabetic nephropathy had slightly lower mean hemoglobin levels prior to undergoing dialysis, compared with those who had nondiabetic renal disease (10.8 vs. 11.0 g/dL, respectively). "It's a small but statistically significant difference," Dr. Ford said. After adjustment for age, gender, ethnicity, and eGFR, "this significant difference remained."

He acknowledged certain limitations of the study, including its observational design and the fact that the data came directly from renal information technology systems, "so we have to rely on the accuracy of what's being sent."

Dr. Ford reported that he had no relevant financial conflicts to disclose. ■

Exenatide Gains Indication For Type 2 Monotherapy

BY ELIZABETH MECHCATIE

The approved indication for exenatide was expanded with the Food and Drug Administration's approval of the glucagon-like peptide-1 (GLP-1) receptor agonist as monotherapy, as an adjunct to diet and exercise in adults with type 2 diabetes, the manufacturer announced.

Previously, exenatide (marketed as Byetta by Amylin Pharmaceuticals Inc. and Eli Lilly & Co.) was approved for type 2 diabetes in combination with diet and exercise and with other diabetes medications.

Approval was based on a study of 232 type 2 diabetes patients who did not achieve adequate glycemic control on diet and exercise alone and were randomized to treatment with one of two exenatide doses or placebo. At 24 weeks, reductions in hemoglobin A_{1c} levels from baseline were significantly greater among those on 5 mcg or 10 mcg of exenatide twice a day compared with those on placebo, according to the revised label.

Nausea, the most common side effect, affected 3% of those on the 5-mcg dose and 13% of those on the 10-mcg dose, according to Amylin's announcement.

In addition to the new indication, the FDA approved changes to the safety information in the exenatide label, including pancreatitis in the warnings and precautions section, which addresses a previous FDA alert, and more information about exenatide use in patients with renal impairment. There have been postmarketing reports of acute pancreatitis associated with exenatide, including cases of fatal and nonfatal hemorrhagic or necrotizing pancreatitis. The label also advises against use of exenatide in patients with severe renal impairment or end-stage renal disease and recommends that it should be used cautiously in patients who have had a kidney transplant.

Exenatide, like other GLP-1 receptors, "enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying," according to the label. Exenatide should be injected subcutaneously within 60 minutes before morning and evening meals, or before the two main meals of the day, about 6 hours or more apart. The recommended starting dose is 5 mcg twice a day, increasing to 10 mcg twice a day after 1 month, depending on the patient's response. ■

The updated safety changes in the label are explained in a "Dear Health Care Professional" letter, which can be viewed at www.byettahcp.com/hcp/pdf/Dear%20HCP%20Letter.pdf.