ApoB Synthesis Inhibitor Cut LDL Cholesterol

BY CAROLINE HELWICK

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – In patients with hypercholesterolemia and high cardiovascular risk, the novel agent mipomersen administered as add-on therapy led to robust reductions in LDL cholesterol, based on the results of a double-blind, phase III study.

"In high-risk patients refractory to maximally tolerated statin therapy, the addition of mipomersen significantly reduced LDL-C and other atherogenic lipids and lipoproteins," said Dr. William C. Cromwell of the Presbyterian Cardiovascular Institute in Charlotte, N.C.

Mipomersen is the first of a new class of agents called apolipoprotein B (apoB) synthesis inhibitors. In the study, the drug was administered subcutaneously once a week. Among its side effects were injection site reactions, increases in alanine aminotransferase (ALT) levels, and steatosis.

The study included 158 patients at high risk for cardiovascular events who were unable to achieve target LDL-C levels with statins, bile-acid sequestrants, and niacin. At baseline, all patients were on maximally tolerated doses of a statin; 63 were on the maximal approved dose, and 25 were also receiving ezetimibe.

All subjects had LDL-C levels of at least 100 mg/dL and triglycerides below 200 mg/dL. They were randomized 2:1 to 200 mg mipomersen or placebo weekly for 26 weeks. The primary end point was percent change in LDL-C from baseline at week 28 or 2 weeks after the last dose if treatment was not completed.

LDL-C levels of less than 100 mg/dL were achieved by 77 (76%) mipomersen-treated patients, compared with 19 (38%) placebo-treated patients. LDL-C levels of less than 70 mg/dL were achieved by 51 (50%) and 4 (8%), respectively.

The percent reduction in LDL cholesterol from baseline to the primary efficacy time point was a 37% drop in the mipomersen arm and a 5% drop in the placebo arm, a significant difference.

"LDL-C levels decreased through the first 17 weeks of treatment and remained relatively low through week 28," Dr. Cromwell observed. "Mipomersen's lipid-lowering effects were independent of baseline LDL-C or race, and were similar for patients with and without diabetes."

The effect of the drug in the diabetic subset was robust. In the diabetes cohort, the mean decline in LDL-C from baseline was 51% for the 56 patients on mipomersen and 32% for the 29 on placebo.

Mipomersen also was associated with significant reductions from baseline values in apoB (38%), total cholesterol (26%), non-HDL cholesterol (36%), and lipoprotein(a) (24%). HDL-C levels did not change significantly from baseline.

Sixty of the 105 mipomersen-treated patients (57%) and 44 of 52 placebo patients (85%) completed treatment. A total of 26 mipomersen-treated patients and 2 placebo-treated patients discontinued as a result of on-treatment adverse events. Of the mipomersen non-completers, seven discontinued because of a liver enzyme-related adverse event, and seven stopped because of an injection site reaction.

Injection site reactions were the most common adverse event, occurring in 78% of the mipomersen group and 31% of the placebo group. Flu-like symptoms occurred in 34% and 21%, respectively. "Injection site reaction is the biggest side effect with this drug. This ranges from induration to redness, and some patients have skin discoloration," Dr. Cromwell acknowledged.

ALT elevations at least 3 times the upper limit of normal were observed in 14% of patients on mipomersen, versus none receiving placebo, but this occurred without concomitant significant bilirubin elevations, he said. For 10% of patients, ALT elevations occurred on consecutive measurements at least 7 days apart.

Approximately one-third of patients had an increase in steatosis, defined as liver fat increasing by at least 5%; median percent change from baseline was 15%. "This does not represent a huge accumulation of fat. Instead, it is a signal that it's there at 28 weeks, and it is not particularly worrying. In a series of patients with much longer exposures, there is a plateau in this increase."

Dr. Patrick Moriarty, a lipid specialist and professor of medicine at the University of Kansas, Kansas City, commented, "We treat many refractory patients, and I can tell you that a drug of this class is very much needed in this patient population. It will help get their lipid numbers down."

The fact that patients achieve good LDL-C reductions on top of statin therapy is very encouraging, he said, noting, "The drug is not for every patient, but it could fill the need for an effective treatment in a small subset."

Dr. Moriarty said the injectable delivery will not be a barrier to acceptance. "Patients can do these injections themselves, just like diabetes patients do. In studies I've participated in, we offer patients the opportunity to have the nurse give them the injections but most patients learn to do [the injections] themselves." ■

VITALS

Major Finding: LDL-C levels of less than 100 mg/dL were achieved by 76% of mipomersen-treated patients and 38% of placebo-treated patients. LDL-C levels of less than 70 mg/dL were achieved by 50% and 8%, respectively.

Data Source: The double-blind study included 158 high-risk patients who were unable to achieve target LDL-C levels on optimal therapy and were randomized 2:1 to 200 mg subcutaneous mipomersen or placebo weekly.

Disclosures: The study was sponsored by Isis Pharmaceuticals and Genzyme Corporation. Dr. Cromwell has received consultant fees or honoraria from Isis. Dr. Moriarty has participated in clinical trials of mipomersen.

Benefits of Lipid-Lowering Agents Persists After Trials End

BY CAROLINE HELWICK

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – In major clinical trials of lipid-lowering agents, the mortality benefit derived from medical therapy persists long after the studies end, according to a meta-analysis presented at the annual meeting of the American College of Cardiology.

Furthermore, placebo recipients who cross over to lipid-lowering therapy in the open-label phases of the studies demonstrate survival benefits as well, but never attain the protection achieved by being randomized to active treatment earlier on, according to Dr. William J. Kostis of Massachusetts General Hospital, Boston. "Persons with risk factors for coronary artery disease should be treated early," Dr. Kostis said in an interview. "The sooner you treat, the better."

He and his colleagues searched several major databases to identify randomized trials of lipid-lowering therapies that also contained an analysis of patient outcomes after the randomized portion of the trials had ended and an open-label phase had begun. Active treatment in the trials involved statins, niacin, cholestyramine, or gemfibrozil.

The analysis included eight clinical trials involving 44,255 patients, of whom 8,144 died during follow-up.

The average patient remained on the assigned treatment for approximately 5 years and was on the lipid-lowering agent in the open-label phase for approximately 6 years.

During the randomized phase of the trials, the mean all-cause mortality was significantly lower for the active treatment group (odds ratio, 0.84), as was cardiovascular mortality (OR, 0.72). The lower mortality among those initially receiving active therapy persisted during the open-label follow-up phase (OR, 0.90), as did the reduction in cardiovascular mortality (OR, 0.82).

"Being treated with a beneficial medication for a longer period of time is better, possibly because we are arresting pathophysiology at an earlier stage," Dr. Kostis proposed. He added that statins may be reducing the size of infarcts in patients who have myocardial infarctions.

Dr. Patrick Moriarty, a lipid specialist and professor of medicine at the University of Kansas in Kansas City, agreed. "We need to start lipid-lowering therapy early to get the most benefit," and this includes interventions in children when necessary, he added.

"We treat pediatric patients all the time," Dr. Moriarty said, "not only those with familial hyperlipidemias but also those with metabolic syndrome. … The future emphasis will be, 'the sooner the better.' " ■

VITALS

Major Finding: During the open-label phase of randomized trials studied, the lower mortality among those who initially received active therapy persisted (odds ratio, 0.90; $P = .0035$), as did the reduction in cardiovascular mortality (OR, 0.82; $P = .0014$).

Data Source: A meta-analysis involving 44,255 patients in eight clinical trials of lipid-lowering therapy. All trials involved an open-label phase after the randomized treatment period ended.

Disclosures: Dr. Kostis and Dr. Moriarty reported having no relevant conflicts of interest.