HDL Soared, LDL Dropped With Anacetrapib

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FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION

CHICAGO – The experimental oral agent anacetrapib increased HDL cholesterol levels by a staggering 138%, compared with placebo, in high-risk patients and did so without the negative side effects that plagued another drug in the same class.

When compared with placebo at 24 weeks, once-daily anacetrapib increased HDL levels from 40 mg/dL to 101 mg/dL and decreased LDL levels by 40% from 81 mg/dL to 45 mg/dL in the double-blind phase III Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib (DEFINE) trial.

"This is a total change in what lipids can be," said senior investigator Dr. Christopher Cannon, who went one step further in a statement describing anacetrapib as having a "knock-your-socks-off effect on HDL and a jaw-dropping effect on LDL" among 1,623 patients already taking a cholesterol-lowering statin and had LDL levels consistent with recommended guidelines.

Anacetrapib is a cholesteryl ester transfer protein (CETP) inhibitor designed to fight hypercholesterolemia by raising levels of HDL. The strategy was called into question, however, after the experimental CETP inhibitor torcetrapib was found to have off-target effects in the adrenal glands, leading to increased blood pressure, mortality, and cardiovascular events.

Anacetrapib had an acceptable side-effect profile, with no effects on blood pressure electrolytes or aldosterone through 76 weeks of follow-up, Dr. Cannon, with Brigham and Women's Hospital, Boston, reported at a press briefing at the meeting. The prespecified, adjudicated composite end point of death from cardiovascular causes, MI, hospitalization for unstable angina, or stroke occurred in 16 anacetrapib-treated patients and in 21 placebo-treated patients.

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DR. CANNON

Although the trial was not designed as an outcome study, a Bayesian analysis indicated a 94% predictive probability that anacetrapib would not increase cardiovascular events by 25% as seen with torcetrapib.

In addition, anacetrapib reduced the need for revascularization by two-thirds, compared with placebo (8 patients vs. 28 patients), a finding that Dr. Cannon said convinced him that the strategy of CETP inhibition works.

The REVEAL follow-up trial of anacetrapib vs. placebo is being launched in Europe, North America, and Asia in 30,000 patients with occlusive arterial disease, with a primary end point of coronary death, MI, or coronary revascularization, Dr. Cannon announced during the press conference.

Reporters questioned whether increasing HDL really matters, to which Dr. Jessup remarked that HDL is a potent marker of risk and that older data showed that niacin, which also works by increasing HDL, decreased the need for revascularization. Two trials of niacin are also underway that may provide more contemporary data.

There is some concern that the drug might be too powerful and potentially push levels too low, as 18% of patients had to discontinue treatment after their LDL cholesterol level fell below 25 mg/dL.

Follow-up from REVEAL is planned in 4 years, which means that barring any new safety signals, anacetrapib would be submitted for approval in about 2015, Dr. Cannon said in an interview.

Results of DEFINE were published online simultaneously with Dr. Cannon's presentation (N. Engl. J. Med. 2010 [doi:10.1056/NEJMoa1009744]). ■

VITALS

Major Finding: At 24 weeks, once-daily anacetrapib increased HDL cholesterol levels from 40 mg/dL to 101 mg/dL and decreased LDL levels from 81 mg/dL to 45 mg/dL, both highly significant differences from placebo.

Data Source: DEFINE, a phase III trial in 1,623 patients with or at high risk for coronary heart disease.

Disclosures: DEFINE was supported by Merck Research Laboratories. Dr. Cannon and his coauthors report financial relationships with several pharmaceutical firms including Merck. Dr. Cannon also serves as an adviser and holds equity in Automedics Medical Systems.