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Evolocumab superior to ezetimibe in lowering LDL cholesterol

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Evolocumab, an injected form of a class of drugs called PCSK9 inhibitors that lower low-density lipoprotein cholesterol, also known as LDL-C or "bad cholesterol," outperformed ezetimibe with few side effects in patients unable to take statins, according to research from GAUSS-2 presented at the American College of Cardiology's 63rd Annual Scientific Session.

High LDL cholesterol is considered a major risk factor for cardiovascular disease. Statins are commonly prescribed to reduce that risk. Currently ezetimibe is one of the few options to lower LDL-C for patients who cannot tolerate statins, but it is less effective than statins in decreasing LDL-C.

GAUSS-2 is a 14-country, 12-week double-blind comparison of subcutaneously administered evolocumab versus oral ezetimibe in patients with high cholesterol who were unable to tolerate effective doses of at least two different statins. In this phase III study, half of patients tried three statins unsuccessfully, and 22 percent couldn't tolerate any of at least four different statin drugs. The patients had a minimum LDL-C level of 193 mg/dL.

A total of 307 patients were randomly assigned to one of two evolocumab regimens (140 mg every two weeks or 420 mg per month, plus daily placebo) or one of two ezetimibe groups (a placebo injection every two weeks or monthly, plus 10 mg oral ezetimibe daily). Mean age was 62 years, and 46 percent of patients were women.

The primary endpoints of LDL-C reductions from baseline were met: 53 percent to 56 percent decrease of LDL-C from baseline at week 12 in evolocumab-treated patients, corresponding to a 37 percent to 39 percent LDL-C decrease with ezetimibe. Musculoskeletal side effects were reported in 12 percent of patients on evolocumab compared to 23 percent on ezetimibe. More than 94 percent of all enrolled patients completed the study. The study drug was stopped because of treatment-related side effects in 8 percent of evolocumab patients and 13 percent of ezetimibe patients. Safety data for evolcumab versus ezetimibe include the following side effects: headache (8 percent vs. 9 percent), muscle pain (8 percent vs. 18 percent), pain in extremities (7 percent vs. 1 percent), muscle spasms (6 percent vs. 4 percent), fatigue (4 percent vs. 10 percent), nausea (4 percent vs. 7 percent), diarrhea (2 percent vs. 7 percent), sensation of tingling, prickling or burning known as paresthesia (1 percent vs. 5 percent). Patients who were taking low-dose statins were more likely to develop muscle pain in both study arms than those who took no statins (evolocumab, 17 percent vs. 6 percent; ezetimibe, 21 percent vs. 17 percent).

"We have a growing population of patients treated with at least two different types of statins who still experience side effects so much they want to discontinue the drug," said Erik S.G. Stroes, M.D., chair and professor at the Department of Vascular Medicine in Amsterdam's Medical Center and the study's principal investigator. "The one big difference between our study and others in patients at increased cardiovascular risk is that for these patients, we don't have a good alternative treatment – no drug with robust LDL-lowering potency and good tolerability. For clinicians trained to solve problems, an unmet clinical need is a big issue."

Earlier studies indicate that more than 75 percent of patients who failed one statin can still do well on a second statin drug. This finding makes patients who have been unable to tolerate two or more statins a

particularly challenging group.

Stroes noted that clinicians have debated whether cardiovascular patients would accept a drug administered by injection, but the study's cardiovascular physicians and internists found few problems with the subcutaneous regimen. Evolocumab must be delivered by this route because it's a fully human monoclonal antibody, a protein that will be broken down in the stomach and bowel if taken orally.

"What's innovative here is that if you give a drug, it's hardly ever specific; statins, for example, can work on a lot of organs," Stroes said. "An antibody is, in and of itself, inert. It binds selectively to a particular sequence on a protein or bacteria and can have a predictable effect on a particular system. That's most likely why evolocumab has a good safety profile with very high efficacy. This study suggests that statin-induced myopathy [muscle discomfort] may be due to another molecular pathway and is not related to LDL-C lowering per se."

There is no generally accepted definition of statin intolerance yet, Stroes said. The GAUSS-3 study, planned to start in the second half of 2014, will include a separate placebo-controlled re-exposure to statin before evolocumab therapy.

"It will help in further delineating statin intolerance and how that should be defined in clinical practice," he said.

Stroes noted two limitations to the study. Reducing LDL-C levels has been demonstrated to translate into a reduced risk of cardiovascular events primarily with statin treatment. The benefit of evolocumab on cardiovascular endpoints awaits the results of the ongoing FOURIER trial. Additionally, the 12-week duration of this study was rather short considering that the majority of patients require life-long treatment to manage LDL-C. The good tolerability observed in this study also needs

confirmation in the ongoing long-term trials, Stroes said.

More information: This study will be simultaneously published online in the *Journal of the American College of Cardiology* at the time of presentation.

Provided by American College of Cardiology