Trial offers objective evidence of muscle-related side effects with statins

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The first major clinical trial to include a blinded, placebo-controlled "statin re-challenge" in patients with a history of muscle-related side effects sheds new light on statin-associated muscle symptoms, according to research presented at the American College of Cardiology's 65th Annual Scientific Session. The trial also demonstrates that monthly self-injection of the relatively new non-statin cholesterol-lowering drug evolocumab reduces levels of low-density lipoprotein, or LDL, cholesterol to a greater extent than ezetimibe, a traditional drug used in statin-intolerant patients.

The study showed that 42.6 percent of 491 patients who had previously reported muscle pain with at least two different statins had a recurrence of symptoms during blinded administration of atorvastatin, but not while taking a placebo.

After a 24-week treatment period, patients with confirmed statin intolerance who were given evolocumab on average showed a 52.8 percent reduction in LDL cholesterol, one of the study's co-primary endpoints, compared with a 16.7 percent reduction for patients taking ezetimibe. For the study's other co-primary endpoint, the average change in LDL cholesterol for weeks 22 and 24, patients taking evolocumab showed a reduction of 54.5 percent and patients taking ezetimibe showed a reduction of 16.7 percent.

"These findings provide unique insights into the challenging clinical problem of muscle symptoms in statin treated patients," said Steven Nissen, M.D., MACC, chairman of Cardiovascular Medicine at Cleveland Clinic and the lead author of the trial. "Evolocumab substantially lowered LDL cholesterol with few patients experiencing muscle symptoms. The study has important implications for both guidelines and regulatory policy, because it provides strong evidence that muscle-related statin intolerance is a real and reproducible phenomenon."

The patients in the GAUSS-3 trial had very high levels of LDL cholesterol, averaging more than 210 mg/dL. Untreated high LDL cholesterol increases the risk of heart disease, and statins are the most effective drugs available, yet some patients report that that they are unable to tolerate statins, mostly due to muscle pain or weakness.

There has been considerable controversy about the prevalence of muscle-related statin intolerance because large randomized trials have reported low rates of muscle symptoms, while observational studies have suggested that 5 to 20 percent of patients experience muscle symptoms when taking statins.

"Statin intolerance has been one of the most vexing problems faced by cardiologists," Nissen said. "Patients with high levels of LDL cholesterol and a high risk of cardiovascular events are often reluctant or completely unwilling to take statins, the only cholesterol lowering drugs approved to reduce their risk of a cardiovascular event. This situation is extremely frustrating for both patients and physicians because there have not been good alternatives for treatment."

Evolocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, is a non-statin cholesterol-lowering drug administered by self-injection every two to four weeks. By binding to and inhibiting PCSK9, a protein that degrades LDL cholesterol receptors on the surface of the liver, the drug is designed to increase the number of LDL receptors on the liver, thus allowing the liver to remove LDL cholesterol from the blood more effectively. Ezetimibe, the existing drug used as a control in the trial, lowers blood cholesterol by decreasing the absorption of cholesterol in the small intestine.

The phase 3, randomized, double-blind GAUSS-3 trial enrolled 511 patients at 53 health care centers. Participants had high LDL cholesterol and a history

of statin intolerance. A vast majority of participants—82 percent—had tried and failed to tolerate three or more statins.

Previous studies, including the trial's predecessor, GAUSS-2, have shown evolocumab reduces LDL cholesterol levels more effectively than ezetimibe.

Because the trial was intended to evaluate evolocumab in statin-intolerant patients, it included an initial statin re-challenge procedure designed to confirm that patients had reproducible muscle symptoms when taking a statin. Nineteen of the enrolled participants bypassed this initial segment because they were documented to have creatine kinase levels—a marker of muscle injury—at least 10 times higher than the upper limit of normal when taking a statin.

Those who participated in the statin challenge were given 20 milligrams of atorvastatin or a placebo daily for 10 weeks, then switched over and were given either a placebo or atorvastatin—whichever one they had not been given in the first phase—for 10 more weeks. Of the 491 participants, 209, or 42.6 percent, reported muscle-related side effects while taking atorvastatin but not while taking the placebo. More than a quarter, 26.5 percent, reported muscle pain while taking the placebo but not while taking atorvastatin, suggesting that although statin intolerance can be confirmed in a substantial proportion of patients with self-reported intolerance, there is also a significant proportion who experience muscle pain that cannot be attributed to taking statins.

After that initial phase, 218 patients with confirmed statin intolerance were enrolled in the trial's second segment, with 145 randomly assigned to receive evolocumab and 73 randomized to receive ezetimibe. Because evolocumab was administered through self-administered injections totaling 420 milligrams per month, and ezetimibe was administered through a 10-milligram daily pill, those randomized to receive evolocumab were given injections of evolocumab and daily placebo pills, and those randomized to receive ezetimibe were given placebo injections and a daily ezetimibe pill.

Participants in the study's second phase had an average baseline LDL cholesterol level of 220 mg/dl. After 24 weeks, those given evolocumab had an LDL cholesterol level of 104 mg/dl on average; 64.1 percent of patients taking evolocumab finished the trial with LDL cholesterol below 100 mg/dl, and 29.9 percent finished with LDL cholesterol below 70 mg/dl.

Treatment was discontinued during the trial for one patient given evolocumab and five patients given ezetimibe due to muscle-related adverse events.

Longer-term results from another evolocumab trial showing health outcomes may be available by the end of 2016.

The study's limitations included its modest size and relatively short duration, but Nissen said it was adequately powered to address its primary endpoint.

The trial was funded by Amgen. Nissen has served as a consultant for many pharmaceutical companies and has overseen clinical trials for Amgen, AstraZeneca, Cerenis, Eli Lilly, Novartis, Novo Nordisk, The Medicines Company, Orexigen, Takeda and Pfizer. However, he does not accept honoraria, consulting fees or other compensation from commercial entities.

This study was simultaneously published online in the *Journal of the American Medical Association* at the time of presentation.

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