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Cholesterol lowering therapies for patients with muscle-related statin intolerance

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Steven E. Nissen, M.D., of the Cleveland Clinic, and colleagues identified patients with muscle-related adverse effects from statins and compared lipid-lowering efficacy for two nonstatin therapies, ezetimibe and evolocumab. The study was published online by *JAMA*, and is being released to coincide with its presentation at the American College of Cardiology's 65th Annual Scientific Session & Expo.

A significant proportion of patients with clinical indications for statin treatment report inability to tolerate evidence-based doses, most commonly because of muscle-related adverse effects, reported by 5 percent to 20 percent of patients. These patients typically report muscle pain or weakness when treatment is initiated or dosage increased and relief when the drug is discontinued or the dosage reduced. Patients with muscle-related intolerance often refuse to take statins despite elevated low-density lipoprotein cholesterol (LDL-C) levels and a high risk of major cardiovascular events. Current management may include very low or intermittent administration of statins or use of ezetimibe, but these strategies seldom achieve reductions recommended by current guidelines.

For this study, the researchers conducted a two-stage randomized clinical trial that included 511 adult patients with uncontrolled LDL-C levels and a history of intolerance to 2 or more statins. Phase A involved a 24-week crossover procedure in which patients were randomly assigned to atorvastatin (20 mg) or placebo to identify patients having symptoms only with atorvastatin but not placebo. In phase B, patients were

randomly assigned to evolocumab (420 mg monthly, by injection) or oral ezetimibe (10 mg daily) for 24 weeks.

In phase A, the researchers observed a 43 percent rate of discontinuation for intolerable muscle symptoms with atorvastatin but not placebo. However, 27 percent of patients reported similar symptoms with placebo but not atorvastatin, demonstrating that reported muscle symptoms are not always related to statin use. "Since statin-associated muscle symptoms are dose-related, the rate observed in [this trial] for atorvastatin (20 mg) may underestimate the problem, particularly for patients needing high-intensity statin therapy, such as those enrolled in the trial."

During the second phase of the study, the authors found that evolocumab produced significantly larger reductions in levels of LDL-C and other lipoproteins compared to ezetimibe. Both coprimary end points (the average percent change in LDL-C level from baseline to the average of weeks 22 and 24 levels and from baseline to week 24 levels) showed a 17 percent reduction with ezetimibe and a more than 50 percent reduction with evolocumab. Despite very high baseline values, the LDL-C goal of less than 70 mg/dL was achieved in nearly 30 percent of evolocumab-treated patients and 1.4 percent of ezetimibe-treated patients.

Muscle symptoms were reported in 29 percent of ezetimibe-treated patients and 21 percent of evolocumab-treated patients. Active study drug was stopped for muscle symptoms in 7 percent of ezetimibe-treated patients and 0.7 percent of evolocumab-treated patients.

"These findings demonstrate that both drugs are unlikely to provoke muscle symptoms and can be administered successfully in such patients, although with significant differences in lipid-lowering efficacy. Since a minority of patients achieved optimal LDL-C levels despite treatment

with evolocumab, it may be worth exploring the addition of ezetimibe to evolocumab for those patients requiring further LDL-C reduction. It should be noted that neither ezetimibe nor evolocumab is approved for reduction of major adverse cardiovascular events," the authors write.

"Further studies are needed to assess long-term efficacy and safety."

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