Ezetimibe's Clinical Benefit Called into Question

Kastelein JJ, Akdim F, Stroes ES, et al; ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008;358:1431–43.

Study Overview

Objective. To evaluate the effect of ezetimibe on progression of atherosclerosis.

Design. Multicenter, randomized, double-blind, controlled trial.

Setting and participants. Between August 2002 and April 2006, 720 patients from 18 ambulatory care centers worldwide with familial hypercholesterolemia and low-density lipoprotein (LDL) cholesterol ≥ 210 mg/dL were randomized to simvastatin 80 mg plus ezetimibe 10 mg or placebo and followed for 24 months. Patients underwent B-mode ultrasonography of intima-media thickness, the results of which served as a measure of atherosclerosis progression.

Main outcome measures. The primary outcome was mean change in carotid artery intima-media thickness from baseline to 24 months. Secondary outcomes included other variables regarding the intima-media thickness of the carotid and femoral arteries. Other important variables included levels of LDL, high-density lipoprotein, and total cholesterol, triglycerides, apolipoprotein B and A1, and C-reactive protein at baseline and 24 months.

Main results. The simvastatin-only group had a mean (± SE) change in carotid artery intima-media thickness of 0.0058 ± 0.0037 mm compared with a mean change of 0.0111 ± 0.0038 mm in the simvastatin plus ezetimibe group; this result was not statistically significant ($P = 0.29$). None of the secondary endpoints differed significantly between the 2 groups. Mean LDL levels were significantly reduced in the simvastatin plus ezetimibe group as compared with the simvastatin-only group (141.3 mg/dL vs. 192.7 mg/dL; $P < 0.01$). Greater reductions were seen in the combined therapy group compared with the simvastatin-only group with regard to triglyceride and C-reactive protein levels (–29.8 mg/dL vs. –23.2 mg/dL [difference, 6.6%] and –49.2 mg/L vs. –23.5 mg/L [difference, 25.7%], respectively; $P < 0.01$ for both comparisons). No differences were seen in side effect or safety profiles between the 2 groups.

Conclusion. Despite decreases in LDL cholesterol, C-reactive protein, and triglyceride levels, the addition of ezetimibe did not significantly reduce progression of atherosclerosis.

Commentary

Although statins have been shown to reduce LDL cholesterol and progression of atherosclerosis, other medications that reduce LDL cholesterol have not been proven to have the same effect on atherosclerosis. The well-designed ENHANCE trial has caused much controversy and raised many questions for both physicians and patients alike. The aforementioned study showed that the addition of ezetimibe did not affect the progression of atherosclerosis despite the favorable effect on lipid profiles. This study should be scrutinized more closely before general conclusions about the efficacy of ezetimibe are made. Patients in this study had a diagnosis of familial hypercholesterolemia and a mean LDL level of 318 mg/dL. Patients did not have coronary artery disease or a history of myocardial infarction, comorbidities common to patients prescribed statins and other lipid-lowering medications.

The study mentions 3 possible explanations for the findings. First, lowering LDL cholesterol by a drug other than a statin may be ineffective for reducing the progression of atherosclerosis. Although statins primarily lower LDL cholesterol by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, they also have anti-inflammatory and vascular endothelial effects that may not be conferred by other lipid-lowering medications. Another possible explanation was that the measurement technique (B-mode ultrasonography) used to assess carotid artery intima-media thickness may not accurately reflect changes in atherosclerotic burden. One must remember that intima-media thickness, much like C-reactive protein and LDL levels, are surrogate endpoints used to measure risk of clinical outcomes such as stroke, myocardial infarction, or cardiovascular death and are not necessarily meaningful clinical outcomes by themselves. Another possibility was that the study population had too low risk for atherosclerosis, which would limit the ability to detect a difference between the 2 groups.

This controversial study was released at the American College of Cardiology conference in March 2008 and resulted in a drop of the manufacturer's (Merck) stock price

shortly thereafter. One question raised was why the U.S. Food and Drug Administration quickly approved a drug that had limited efficacy based on the surrogate endpoint of LDL reduction. Another question is whether direct-to-consumer advertising of Vytorin (ezetimibe/simvastatin; Merck/Schering-Plough Pharmaceuticals, North Wales, PA) is ethical, given that these data on efficacy were probably available to the drug companies before the results of the study were released. This study seems to indicate that all LDL reduction is not equal and that drug choice is important when attempting to lower LDL cholesterol.

Applications for Clinical Practice

For now, lifestyle modification and statins are the therapeutic modalities of choice for lowering LDL cholesterol and have been shown to improve clinical outcomes. Practitioners should try to maximize the dosing of statins unless side effects stop titration. Niacin, omega-3 fatty acids, and fibrates are other alternatives to reduce LDL cholesterol. Ezetimibe may be another way to reduce LDL; however, the impact on clinical outcomes is still in question. The ongoing IMPROVE-IT trial [1] will answer this question, but it will likely take years before this study is complete.

—Review by Robert L. Huang, MD, MPH

Reference

1. O'Riordan M. Ezetimibe controversy continues: IMPROVE-IT enlarge and delayed, the inside struggle over ENHANCE. HeartWire News; 31 Mar 2008. Available at www.theheart.org/article/852455.do. Accessed 9 May 2008.