Clinical Trials

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Trial Summary

Summary Questions

Title: Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients With Heterozygous Familial Hypercholesterolemia (ENHANCE)
Trial Sponsor: Merck/Schering-Plough
Year Presented: 2008
Summary Posted: 1/14/2008
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Author Disclosure: This author has nothing to disclose.
Reviewer: Deepak L. Bhatt, M.D., F.A.C.C.
Author Disclosure: Research Grants: Sanofi Aventis, Significant (>= $10,000); Research Grants: Heartscape, Significant (>= $10,000); Research Grants: Bristol Myers Squibb, Significant (>= $10,000); Research Grants: The Medicines Company, Significant (>= $10,000); Research Grants: Eisai, Significant (>= $10,000); Research Grants: Ethicon, Significant (>= $10,000)
Issued: January 2008, **CE Term of Approval:** January 2010
Question Status: 1 of 1 answered Start Over CE

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Learning Objective(s): At the conclusion, the learner will describe the changes (as compared to baseline) in carotid intimal medial thickness associated with a statin alone and a statin in combination with ezetimibe the LDL-C reductions in the two treatment arms in the ENHANCE Trial.

Description
The following information was derived from a Merck/Schering-Plough press release from January 14, 2008; full data are to be presented at the 2008 ACC Scientific Session.

Hypothesis
The goal of this trial was to compare the mean change in the intima-media thickness (IMT) measured at three sites in the carotid arteries between patients with Heterozygous Familial Hypercholesterolemia (HeFH) treated with ezetimibe/simvastatin 10/80 mg versus patients treated with high-dose simvastatin 80 mg alone over a two-year period.

Principal Findings
A total of 720 patients with HeFH were randomized in this multinational, randomized, double-blind, active comparator trial: 357 to the ezetimibe/simvastatin arm and 363 to the high-dose simvastatin arm. Images were obtained from the right and left carotid arteries at three sites at baseline, 6, 12, 18, and 24 months. The baseline low-density lipoprotein (LDL) cholesterol levels between the two arms were comparable (319 vs. 318 mg/dl; p=non-significant [NS]). Approximately 80% of patients enrolled in the trial had been on statins previously. The baseline mean carotid IMT measurements were similar between the two arms.

There was no statistically significant difference between the two arms with respect to the primary endpoint, the mean change in carotid IMT. The change from baseline for the ezetimibe/simvastatin arm was 0.0111 mm, compared with 0.0058 mm for the high-dose simvastatin arm (p=0.29).

There was no difference in the incidence of cardiovascular clinical events: cardiovascular deaths (0.6 vs. 0.3%), non-fatal myocardial infarction (0.8% vs. 0.6%), non-fatal stroke (0.3% vs. 0.3%), and need for revascularization (1.7% vs. 1.4%) [p=NS for all]. There was, however, a significant reduction in LDL lowering noted in the ezetimibe/simvastatin arm compared with the simvastatin arm (58% vs. 41%; p<0.01).

The overall incidence of treatment-related adverse events was similar between the two groups: consecutive elevations of serum transaminases ≥ 3X ULN (2.8% vs. 2.2%), elevated CPK ≥ 10 X ULN (1.1% vs. 2.2%), and elevated CPK ≥ 10X ULN with muscle symptoms (0.6% vs. 0.3%) [p=NS for all]. There were no cases of rhabdomyolysis reported in either arm.

Interpretation
The results of the multicenter, randomized ENHANCE trial seem to suggest that in patients with very high baseline LDL levels, such as those with heterozygous familial hypercholesterolemia, the combination of ezetimibe/simvastatin 10/80 mg does not result in significant changes in the mean carotid IMT at 2 years when compared with high-dose simvastatin 80 mg alone. There was also no difference in the incidence of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, or need for revascularization, although this study was not powered to study clinical outcomes. The LDL-lowering effect of ezetimibe/simvastatin was greater than that achieved with high-dose simvastatin alone. Although this was a negative study, it will be interesting to see if larger ongoing trials will be able to demonstrate any relative superiority of the combination of ezetimibe/simvastatin in improving cardiovascular outcomes in high-risk patients as compared with simvastatin alone.

Study Design

Randomized. Blinded. Parallel.
Patients Enrolled: 720
Mean Follow-Up: 24 months

Summary | Questions

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