

After ENHANCE: the cholesterol hypothesis is alive and well

Ian R Hamilton-Craig

Trials measuring major cardiovascular events as an endpoint are the best evidence to determine if an intervention such as ezetimibe conveys benefit

At an American College of Cardiology meeting in Chicago earlier this year, the long-awaited results of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial were finally presented, with simultaneous publication in the *New England Journal of Medicine*.¹

ENHANCE was a double-blind, randomised controlled trial comparing 80 mg of simvastatin plus placebo daily with 80 mg of simvastatin plus 10 mg of ezetimibe daily in patients with familial hypercholesterolaemia. The primary trial endpoint was change in mean carotid and femoral intima-media thickness (IMT) over a 24-month period (Box). Although the trial finished in mid 2006, the results were not forthcoming from the United States sponsors (Merck and Schering-Plough) until a US Congressional Committee required the companies to reveal them, which they did in the form of a press release earlier this year.^{2,3}

In the combined-therapy group, the benefit expected from a 17% lower level of low-density lipoprotein cholesterol (LDL-C) due to ezetimibe was not realised — mean IMT did not differ between the two groups. There was progression in mean carotid IMT (CIMT) in both groups ($P = 0.02$ for simvastatin-only group and $P < 0.01$ for combined-therapy group). Regression occurred in 44.4% of the simvastatin-only group and 45.3% of the combined-therapy group. New lesions (> 1.3 mm CIMT) occurred in 2.8% of the simvastatin-only group and 4.7% of the combined-therapy group ($P = 0.20$).

Various possible explanations for these unexpected results were given by the study authors.¹ The first was that ezetimibe is not protective for the vasculature, in spite of its significant lowering of LDL-C levels; the second was that the methodology used to measure IMT was insufficient to detect small changes in response to the therapy; and the third was that the population with familial hypercholesterolaemia had virtually normal baseline IMT due to their previous extensive treatment with statins, which may have rendered their arteries relatively unresponsive to further LDL-C reduction.

The first explanation is unlikely because ezetimibe has shown no previous evidence of vascular toxicity, and a recent study in which statin–ezetimibe therapy was used as part of an aggressive management algorithm showed regression of CIMT (although this was not a randomised trial of ezetimibe use).⁴ The second explanation is also unlikely, although ENHANCE did not employ electrocardiogram gating of images to control for image variability during the cardiac cycle, and used single-frame technology rather than cine-loop technology to improve image quality.²

The third explanation seems the most likely, for several reasons. Previous studies of CIMT have shown either lack of progression (ie, stabilisation) or regression with lipid-modifying therapy, primarily related to changes in LDL-C levels.⁵ Unlike ENHANCE, these studies involved patients with increased base-

Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study¹

- 720 patients with familial hypercholesterolaemia
- Baseline: low-density lipoprotein (LDL) cholesterol, 8.2 mmol/L; high-density lipoprotein (HDL) cholesterol, 1.2 mmol/L
- Compared simvastatin 80 mg + placebo daily with simvastatin 80 mg + ezetimibe 10 mg daily
- Primary endpoint was mean intima-media thickness (IMT) of carotid and femoral arteries with B-mode ultrasonography
- End of study: mean LDL cholesterol 16.5% lower in ezetimibe group ($P < 0.01$); no difference in HDL cholesterol
- No difference between treatment groups in carotid IMT after 2 years ($P = 0.29$):
 - +0.0058 mm in simvastatin–placebo group
 - +0.011 mm in simvastatin–ezetimibe group
- Side-effect and safety profiles similar in both groups ◆

line CIMT and had inclusion criteria for CIMT. Data also presented at the American College of Cardiology meeting, but yet to be published, showed that statin-naïve patients had no significant change in CIMT with either therapy.² Baseline CIMT in this group was also near-normal — an unusual finding for true familial hypercholesterolaemia patients. However, no data were presented to confirm the presence of LDL receptor mutations.

If this explanation is correct, perhaps ENHANCE could never have shown a positive result, because most patients had been treated with statins for decades before enrolment in the trial. Evidence for this theory comes from the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) extension study, in which patients in the earlier ASAP trial were continued on 80 mg of atorvastatin daily for a further 2 years.⁶ Patients in the original atorvastatin group (in whom there had been regression of 0.031 mm) showed no further change in CIMT, while those originally in the simvastatin 40 mg group (in whom there had been progression of 0.036 mm) showed significant regression.⁶

The results of the ENHANCE trial are important because ezetimibe accounts for a significant proportion of lipid-lowering medication prescriptions around the world (3% in Canada, similar to use in Australia; and 15% in the US).⁷ Ezetimibe was approved for marketing in the US about 5 years ago, based on its efficacy in lowering LDL-C levels rather than efficacy in reducing major adverse cardiovascular events or improving surrogate endpoints such as CIMT. This situation is the opposite for newer drugs such as torcetrapib, which, in spite of increasing high-density lipoprotein cholesterol levels by more than 50%, was withdrawn from the market because of negative results in trials investigating its effects on CIMT and major adverse cardiovascular events.^{8,9}

So, where do we go from here? The first caveat is not to abandon the modern cholesterol hypothesis (“the lower the LDL-C, the better”) after one negative trial. Only trials measuring major adverse cardiovascular events as an endpoint can definitively answer the question of whether a given intervention conveys benefit, regardless of changes in surrogate markers like CIMT or plaque size. We must therefore await the results of a clinical endpoint trial with ezetimibe, which adds a further 15%–20% reduction in LDL-C levels to that achieved by statin therapy, and which should reduce major adverse cardiovascular events by a similar percentage. IMPROVE-IT is a trial comparing cardiovascular death, major coronary events and stroke in 18 000 patients with recent acute coronary syndromes treated with 40 mg of simvastatin either alone or in combination with 10 mg of ezetimibe.² It is due to be reported in 2012. Until then, it seems prudent to continue clinical practice on the basis that the cholesterol hypothesis is alive and well, and to continue using ezetimibe in statin-intolerant patients and those taking maximum-tolerated doses of statins who have not yet achieved LDL-C target levels.¹⁰

Competing interests

Ian Hamilton-Craig has received financial support to attend and give presentations at scientific meetings from AstraZeneca, Merck Sharp & Dohme, Schering-Plough, Pfizer, Bristol-Myers Squibb, Solvay, Sanofi-Aventis, Novartis and Abbott (Australia). He is a member of the Lipid Advisory Board of Merck Sharp & Dohme/Schering-Plough, AstraZeneca and Solvay, the Familial Hypercholesterolaemia Committee of the Australian Atherosclerosis Society, and the Council on Genetic Cardiovascular Diseases of the Cardiac Society of Australia and New Zealand.

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