The Implications of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression Trial: A Return to First Principles

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ABSTRACT

To outward appearances, the publication of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial has led to a monolithic backlash against the use of ezetimibe by cardiologists for the treatment of hyperlipidemia. Rather than be swayed by popular opinion, we should each put the results of ENHANCE into context and ask the questions: should I put my trust in an imaging surrogate or in low-density lipoprotein (LDL) cholesterol (LDL-C), and how do the safety and efficacy of ezetimibe compare with other nonstatin lipid-lowering agents?

Key words: ENHANCE trial, ezetimibe, hypercholesterolemia

At the American College of Cardiology's (ACC) Scientific Session in Chicago, Illinois, in late March 2008, the cardiology community was finally able to see the long-delayed analysis of the results from the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, comparing the effects of treatment with 80 mg of Simvastatin daily alone versus 80 mg of Simvastatin and 10 mg of ezetimibe daily on carotid intima-media thickness (CIMT) in patients with familial hypercholesterolemia.¹ As announced in January 2008, there is no significant difference seen between the 2 treatments, which has led many to question—both privately as well as in the press—whether ezetimibe has any clinical utility and whether it should be prescribed to patients.

As judged by reporting in the press, the expert panel convened at the Scientific Sessions to address the implications of the study took a firm stand against ezetimibe, urging that practitioners generally abandon the medication in favor of statin drugs that have been proven to be of clinical benefit in the primary and secondary prevention of coronary disease. One panel member stated that “. . . as a panel, we would underscore a return to the first principles of medicine.”

Sage advice, to be sure. But a measured consideration of these first principles has been lacking amidst the controversy, politicization, and plain misunderstanding (with CNN announcing that the “. . . popular cholesterol drug fails to improve heart disease,” although the trial was never intended to assess clinical outcomes) surrounding the ENHANCE trial. Let us take a step back and ask the 2 questions most important for practitioners who now have

to decide about continuing to prescribe ezetimibe to their patients:

1. Which endpoints do we trust more as a proxy for clinical outcome—CIMT, or low-density lipoprotein (LDL) cholesterol (LDL-C)?
2. Regarding the strength of the available evidence, how does ezetimibe compare with nonstatin lipid-lowering medications?

CIMT or LDL-C?

The addition of ezetimibe to Simvastatin was unequivocally successful in reducing LDL-C levels, with an incremental 17% reduction in the mean LDL-C level, which for the study population of individuals with familial hypercholesterolemia translated into a reduction in mean LDL-C levels from 193 mg/dL to 141 mg/dL. In contrast, there was essentially no difference in the change in CIMT over the study period (2 y) in the 2 treatment groups. Participants receiving only simvastatin had a mean increase of 0.006 mm (95% confidence interval 0.002 to 0.010 mm), as compared with participants receiving both simvastatin and ezetimibe, who had a mean increase of 0.011 mm (95% confidence interval 0.007 to 0.018 mm). To place these numbers in perspective, the mean CIMT for both groups was 0.70 mm—putting the observed changes in the neighborhood of 1% of the quantity being measured.

Thus, the ENHANCE controversy can be reduced to a discrepancy in the effects of ezetimibe on LDL-C, CRP levels, and CIMT.

How much faith can we put in the CIMT numbers being relevant to the clinical efficacy of ezetimibe (i.e., the reduction of cardiovascular outcomes such as mortality and nonfatal myocardial infarction)? A consideration of other lipid-lowering trials using CIMT as an outcome is instructive.

The trial most similar to ENHANCE was the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study, which compared 80 mg of atorvastatin daily versus 40 mg of simvastatin daily, with CIMT as the primary outcome.² As with ENHANCE, ASAP included patients with familial hypercholesterolemia on treatment for ~ 2 y. Notably, ASAP showed that there was significant progression (0.03 mm) of atherosclerosis with the moderate dose of Simvastatin—far more than that seen with either treatment arm of the ENHANCE trial. Despite the observed progression of atherosclerosis, we know that even moderate dosing of Simvastatin improves outcomes in high-risk individuals. While that dose may not minimize CIMT progression, it may do something even more important—promoting plaque stabilization, which is more difficult to assess.

The Measuring Effects on Intima-media Thickness: an Evaluation of Rosuvastatin (METEOR) trial compared the effect of very high-intensity statin therapy, 40 mg of rosuvastatin daily, versus placebo on CIMT over 2 y.³ Although there were differences in the CIMT protocols used in METEOR versus ENHANCE or ASAP, what was notable was that there was no significant change in CIMT seen in the group that received rosuvastatin, despite a 49% reduction in mean LDL-C level, greater than that seen with Simvastatin in ENHANCE. This finding also suggests that with increased LDL-C lowering, the predominant effect may not be on the change in size of atherosclerotic plaque, but some other aspect of plaque that alters its vulnerability to rupture.

This was borne by the just published Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: A Magnetic Imaging Observation (ORION) trial, in which carotid atherosclerotic plaque was assessed by magnetic resonance imaging.⁴ In the ORION trial, individuals who were on very high-intensity therapy, 40–80 mg of rosuvastatin daily, experienced no change in carotid plaque volume. Rather, in all these individuals with a lipid-rich necrotic core at baseline, there was a mean decrease of 41% in the proportion of the vessel wall composed of the lipid-rich necrotic core. Thus, the predominant benefit derived from statins is likely through stabilization of lipid-laden plaques.

Carotid intima-media thickness measurement, as traditionally practiced, cannot assess changes in plaque composition. This raises the question of whether CIMT is the most appropriate imaging technique to provide a proxy endpoint for clinical outcomes in trials with intensive lowering of LDL-C levels. It is plausible that even though there is no significant difference in CIMT with the use of ezetimibe, there may well be an important change in composition of the

early plaques that could not be measured in the ENHANCE trial.

Even more concerning are issues with CIMT measurement that are specific to the ENHANCE trial. Approximately 17% of the internal CIMT images obtained from study participants were discarded for the final analysis; thus, it is likely that some of the retained images were of borderline quality. Furthermore, the baseline mean CIMT in ENHANCE was 0.70 mm, significantly less than the baseline mean CIMT in ASAP, which was 0.92 mm. The best explanation for this discrepancy is that 80% of the ENHANCE participants had been on lipid-lowering therapy in the past, which likely altered the natural history of the carotid disease in these patients (size, composition, etc.) and affected how CIMT responded to further therapy.

In contrast to CIMT, there is a large body of literature now showing a correlation between extent of reduction of LDL-C levels and improvement in clinical outcomes in both primary and secondary prevention patients, with the caveat that virtually all those trials used statin therapies for LDL-C reduction. The recent announcement of the premature termination of the Randomized Trial of Rosuvastatin in the Primary Prevention of Cardiovascular Events Among Individuals with Low Levels of LDL-C and Elevated Levels of CRP (JUPITER) trial due to greater-than-expected clinical benefit seen with 20 mg of rosuvastatin versus placebo, a dose we know is not associated with CIMT regression, underscores the notion that changes in LDL-C levels are a more faithful proxy for clinical outcomes than CIMT.⁵ While one interpretation of the JUPITER results will undoubtedly be that the clinical benefits accrued from a reduction of CRP rather than LDL-C, it is worth noting that in the ENHANCE trial ezetimibe conferred an incremental 26% reduction in the mean CRP level.

In the absence of any firm clinical outcomes data with ezetimibe, we will have to wait until the completion of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) to know whether the LDL-C changes or the lack of CIMT changes are more reflective of the clinical effects of ezetimibe.⁶ Unfortunately, the intense media attention surrounding the ENHANCE trial will only make it harder for the IMPROVE-IT investigators to recruit and retain participants into their study, which will delay this badly needed information.

Ezetimibe or Other Lipid-lowering Drugs?

Even before the ENHANCE results were announced, it was recommended that statins be the first choice for lipid-lowering therapy in high-risk individuals, given the great weight of data in support of statins. Although some practitioners may have been prescribing ezetimibe or vytorin to patients as initial therapy rather than titrating statins to the maximally tolerated dose, there was never any evidence, and there remains no evidence, that this was a

defensible strategy. If nothing else, the ENHANCE trial has refocused our attention on statins as the preferred therapy for dyslipidemic patients.

What should we do for patients in whom we are not able to achieve the National Cholesterol Education Program Adult Treatment Panel III LDL-C goals with statin therapy alone, especially for the significant minority of patients who can only tolerate low-intensity therapy or cannot tolerate statin therapy at all? Ezetimibe has a very favorable profile as a lipid-lowering medication. It is clearly useful in helping many patients reach LDL-C goals, offering a 15%–25% incremental decrease in LDL-C levels when added to statin therapy.

Ezetimibe is a well tolerated drug, certainly better than other lipid-lowering agents such as niacin, fibrates, and resin, and possibly even better than statins. There are no safety concerns, a point reinforced by the lack of adverse effects documented in the ENHANCE trial. Its only real problem is that clinical outcome data are still pending.

Lest we forget, no other lipid-lowering agent as an adjunctive agent to statin therapy has good outcomes data to date. The combination of Simvastatin and niacin used in secondary prevention patients in the high-density lipoprotein (HDL)-Atherosclerosis Treatment Study (HATS) resulted in an 89% reduction in cardiovascular events; however, the comparison group received a placebo rather than a statin as solo therapy.⁷ While these data with niacin are encouraging, they do not demonstrate an incremental benefit for niacin.

A trial comparing Simvastatin alone with a combination of Simvastatin and extended-release niacin, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study is underway, with the full results not expected until 2011.⁸ It is tempting to extrapolate from the HATS trial, and predict that the AIM-HIGH study will show an extra benefit from niacin, and on that basis conclude that niacin should be our primary second-choice agent. But as practitioners we have to be careful not to fall into the same potential trap as with the ENHANCE trial, assuming the results of the study before the data has been collected.

There have been no large trials comparing a statin with a statin-fibrate combination, and the withdrawal of cerivastatin from the market due to increased rhabdomyolysis when used in combination with gemfibrozil has raised concerns about routinely using the latter agent with other statins. Nor does the lack of reduction in coronary events or mortality with fenofibrate in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial inspire confidence that the combination of a statin and fenofibrate will be better in improving outcomes than statin alone.⁹ Nevertheless,

this proposition is being evaluated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,¹⁰ with the results expected in 2010. Finally, there is no large trial with the combination of a statin and a resin, and it is too poorly tolerated to be practical for routine use.

It is hard not to conclude that ezetimibe is still a reasonable choice for a second-line, lipid-lowering agent in persons on a maximally tolerated dose of a potent statin and who are not at their LDL-C or non-HDL-C goals, as 1 among several suboptimal alternatives, while we await the results of the IMPROVE-IT, AIM-HIGH, and ACCORD trials over the next few years. Certainly there is no reason that, in returning to “first principles,” we should ask all our patients to tear up their prescriptions for ezetimibe.

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