Utility of Ezetimibe

Hiroshi Ashikaga, MD, PhD, Roger S. Blumenthal, MD, and Steven R. Jones, MD

Ezetimibe is the first of a new class of drugs that inhibit cholesterol absorption through the proximal small intestine. It provides an additional 15% to 20% reduction in low-density lipoprotein (LDL) cholesterol in those already taking lipid-lowering medications, and it is widely used as an adjunctive agent in patients taking maximally tolerated doses of statins with suboptimal LDL cholesterol levels. However, since the announcement of the Effect of Combination Ezetimibe and High-Dose Simvastatin Alone on the Atherosclerotic Process in Subjects With Familial Hypercholesterolemia (ENHANCE) trial,1 the clinical utility of ezetimibe has become uncertain to practicing physicians, because of the lack of evidence with hard clinical end points.

The ENHANCE trial was a double-blind, randomized controlled trial comparing simvastatin 80 mg with either placebo or ezetimibe 10 mg in 720 subjects with familial hypercholesterolemia. Although the addition of ezetimibe significantly reduced LDL cholesterol and high-sensitivity C-reactive protein levels, there was no difference in the change in carotid intima-media thickness (CIMT) over 2 years. The results were very disappointing and called into question whether the agent would indeed have an antiatherosclerotic effect and reduce clinical cardiovascular events.

Fleg et al2 provided additional insights into the clinical utility of ezetimibe by presenting a secondary analysis from the Stop Atherosclerosis in Native Diabetes Study (SANDS). SANDS3 was a randomized controlled trial of 499 Native American with type 2 diabetes comparing aggressive and standard treatment strategies. The standard group was treated to conventional goals for LDL cholesterol (100 mg/dl), non–high-density lipoprotein (HDL) cholesterol (130 mg/dl), and systolic blood pressure (130 mm Hg) and the aggressive group to goals of 70 mg/dl, 100 mg/dl, and 115 mm Hg, respectively. Ezetimibe was added if the LDL cholesterol goal was not accomplished with lifestyle modification and statin therapy. The investigators found that the aggressive strategy resulted in the regression of CIMT and greater decreases in left ventricular mass, but clinical events did not differ significantly between the groups.

In the secondary analysis, Fleg et al2 divided the aggressive group into 2 cohorts, those who did and did not receive ezetimibe, and found a similar regression of CIMT at 3 years, rather than 2 years for the ENHANCE trial, in subjects who attained equivalent LDL cholesterol reductions from a statin alone or a statin plus ezetimibe. CIMT in the standard group showed progression rather than regression at 3 years. Although available for non-HDL cholesterol management if required, there was very little use of fibrates or niacin to confound analysis of the 2 strategies. In the aggressive treatment arm, ezetimibe was used in about 1/3 of subjects to achieve goal lipid levels, with target LDL cholesterol <70 mg/dl and non-HDL cholesterol <100 mg/dl, while this target was achieved in about 2/3 of subjects with statin monotherapy.

The results of the SANDS substudy2 require careful interpretation. It was a secondary, nonrandomized, observational study of highly selected subjects who required more lipid lowering than what a statin could provide to achieve the LDL cholesterol goal, and the baseline characteristics were different between the subgroups. In addition, the sample size was modest, and the study was underpowered to detect differences among groups. Nevertheless, the results support the concept that ezetimibe may indeed have an antiatherosclerotic effect. The results are also reassuring, because the study paralleled the real-life treatment of patients using successive agents to predefined treatment goals.

The evidence to date favors the initial use of statins, titrated as needed to target LDL cholesterol and non-HDL cholesterol goals. Most physicians will choose to add a second agent, such as ezetimibe, if further LDL cholesterol lowering is needed after statin titration. Thus, although this was not a trial of a statin versus a statin plus ezetimibe, it shows that essentially identical CIMT outcomes can be achieved with the 2 treatment strategies to achieve a common lipid goal. It is notable that the standard treatment strategy was associated with the progression of atherosclerosis at 3 years, whereas the aggressive strategy yielded a modest regression, supporting the wider use of the optional Adult Treatment Panel III intensive goals in patients with diabetes.

The SANDS substudy comes at an important time, given the intense controversy raised by the ENHANCE trial. The 2 trials are not really comparable, because they assessed 2 very different patient populations with very different lipid disorders using entirely different study designs. One major difference is the on-treatment LDL cholesterol and non-HDL cholesterol levels achieved with a statin compared with a statin plus ezetimibe. Along with other potentially confounding factors, the ENHANCE subjects had on-treatment non-HDL cholesterol levels well above any currently accepted secondary prevention guideline treatment goals: 220 mg/dl on simvastatin alone and 166 mg/dl on combined simvastatin plus ezetimibe. On the basis of previous trials, high non-HDL cholesterol levels in this range would be expected to result in the progression of atherosclerosis or increasing CIMT in the 2 groups. In contrast, the 2 drug treatment strategies in SANDS were compared at low, secondary prevention non-HDL cholesterol levels of approximately 100 mg/dl, the range in which at least CIMT stabilization or, more likely, regression should occur.

So, what should clinicians do with ezetimibe? Ezetimibe is yet to have the long-standing, strong evidence base for clinical efficacy and safety in trials that other lipid-lowering drugs do.4–11 The use of ezetimibe has been driven primar-
ily by the substantially better patient tolerance and convenience of administration of ezetimibe compared with these agents, not clinical outcomes. Ongoing clinical trials such as the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), comparing simvastatin and ezetimibe with simvastatin alone, will provide important insights into the effect of ezetimibe on hard clinical events. In the meantime, although it is reasonable to expect that the LDL cholesterol and apolipoprotein B-100 reductions obtained with ezetimibe should provide similar risk reduction as other agents, an evidence-based agent should be considered first when selecting a second drug after a statin. In patients who are unable or unlikely to tolerate 1 of the evidence-based, known efficacious agents as an add-on to statin therapy, the SANDS substudy provides support for the current judicious use of ezetimibe as an alternative for use after optimized high-dose statin therapy is used to achieve intensive lipid-lowering goals according to existing national guidelines.