Lowering LDL Cholesterol Is Good, but How and in Whom?

Neil J. Stone, M.D., and Donald M. Lloyd-Jones, M.D.

Genetic findings reported approximately 9 years ago in the Journal indicated that rare sequence variants in the gene encoding proprotein convertase subtilisin–kexin type 9 serine protease (PCSK9) were associated with significantly lower long-term plasma levels of low-density lipoprotein (LDL) cholesterol. The observed reduction in LDL cholesterol levels was similar to that attained with moderate-intensity statin therapy. The benefits of lifelong lowering of LDL cholesterol levels were substantial; a 47 to 88% lower risk of coronary heart disease was observed over a period of 15 years in middle-aged persons with such genetic polymorphisms. Further genetic studies indicated that PCSK9 activity was a major determinant of plasma levels of LDL cholesterol in humans.

Two reports now published in the Journal describe the results of long-term studies of treatment with monoclonal antibodies to PCSK9 to lower LDL cholesterol levels. One trial, entitled Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM), was a double-blind, randomized, controlled trial of alirocumab (150 mg administered subcutaneously every 2 weeks) versus placebo in 2341 patients at high risk for cardiovascular events who were already receiving the maximum tolerated doses of statins.

Two other trials, entitled Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1 (OSLER-1) and OSLER-2, used a randomized, open-label design in a total of 4465 patients with various degrees of cardiovascular risk. Evolocumab, administered subcutaneously at a dose of 140 mg every 2 weeks or 420 mg monthly, was added to standard therapy and compared with standard therapy alone over a period of approximately 1 year; the two OSLER trials were analyzed together.

Both the ODYSSEY LONG TERM trial and the OSLER trials included a mix of patients with cardiovascular disease, cardiovascular risk factors, or heterozygous familial hypercholesterolemia, and both included patients with elevated LDL cholesterol values despite statin use. As compared with placebo or standard therapy, the intervention reduced LDL cholesterol levels by an average of 61 to 62%. As with statins, levels of apolipoprotein B, non–high-density lipoprotein (HDL) cholesterol, and triglycerides were lowered by treatment, and levels of apolipoprotein A1 and HDL cholesterol were increased. However, unlike with statins, significant reductions in lipoprotein(a) were also observed.

Because PCSK9 inhibitors allow the achievement of lower LDL cholesterol levels than those achieved to date with statins, a close look at safety is a paramount consideration. Both studies showed no excess of adverse effects overall or in those who had an LDL cholesterol level of less than 25 mg per deciliter (0.6 mmol per liter), but the follow-up period was relatively short. Both studies acknowledged that specific assessment of neurocognitive function is needed.

What’s new? Both studies provide post hoc analyses showing approximately 50% reductions in composite cardiovascular events at 12 to 18 months. In the ODYSSEY LONG TERM trial, the rate of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization was 3.3% in the placebo group and 1.7% in the intervention group. In the OSLER...
trials, the rate of cardiovascular events was 2.18% in the standard-therapy group and 0.95% in the intervention group. In previous trials of statins, the decrease in the event rate was greater in years 2 and 3 than in year 1. With the potential for improved adherence and a greater reduction in LDL cholesterol levels, the data from larger, longer studies of PCSK9 inhibitors could be compelling; such trials are now ongoing.

The ODYSSEY LONG TERM and OSLER studies whet our appetites for further results that show cardiovascular benefit and documented safety, even at substantially lower LDL cholesterol ranges than achieved before. However, it would be premature to endorse these drugs for widespread use before the ongoing randomized trials, appropriately powered for primary endpoint analysis and safety assessment, are available. Reports from several lipid treatment trials provide important object lessons in this regard. Two trials of niacin revealed lower levels of LDL cholesterol and lipoprotein(a) when niacin was added to statin therapy but no net clinical benefit and very worrisome signals of harm. A randomized, controlled trial of torcetrapib reminds us that “off-target” effects can scuttle a promising drug. And the recent long-awaited presentation of results of a trial in which ezetimibe was added to moderate-intensity statin therapy in high-risk patients showed only modest benefit, though with excellent safety.

All these results, including the current ones, fit well into the framework established by the 2013 cholesterol guidelines of the American College of Cardiology and the American Heart Association, which recommended that non-statins could be used in higher-risk patients in whom statin therapy did not lower LDL cholesterol levels sufficiently or in patients with unacceptable side effects from statin therapy, with a strong preference for use of non-statins that have been determined to be safe and effective in randomized, controlled trials. The evidence-driven cholesterol guidelines did not endorse the concept that lower LDL cholesterol levels are better at all costs. They emphasized that, while lower is better, it matters how you get there and whether the benefits outweigh the risks for that patient.

Much work remains to be done, but PCSK9 inhibitors appear on track to become important arrows in our quiver for targeting reduction of cardiovascular events among higher-risk patients when statins are not enough.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Departments of Medicine and Preventive Medicine and the Bluhm Cardiovascular Institute, Feinberg School of Medicine, Northwestern University, Chicago.

This article was published on March 15, 2015, at NEJM.org.


DOI: 10.1056/NEJMe1502192
Copyright © 2015 Massachusetts Medical Society.