Factoring in ANGPTL3 When LDL Is Refractory

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Patients with familial hypercholesterolemia, who have a severely increased low-density lipoprotein (LDL) cholesterol level from birth and are at high risk for premature cardiovascular disease, have inspired and contributed to major advances in lipid therapeutics. A notable example is the drug class targeting proprotein convertase subtilisin–kexin type 9 (PCSK9). Overactivity of PCSK9, which promotes LDL receptor degradation, was discovered to be a cause of familial hypercholesterolemia.1 The addition of a PCSK9 inhibitor to statin therapy can lower the LDL cholesterol level by 60% and reduce cardiovascular risk.2 Reduction of cardiovascular risk with PCSK9 inhibitors is correlated with absolute lowering of the LDL cholesterol level to less than 10 mg per deciliter (0.26 mmol per liter).3 In patients who attain a low LDL cholesterol level, the use of PCSK9 inhibitors appears to be safe. These findings, together with evidence supporting the addition of ezetimibe to statin therapy after acute coronary syndrome, moved clinical lipid management beyond statin monotherapy to combination therapy with the goal of a low LDL cholesterol level. The 2018 American Heart Association–American College of Cardiology guidelines introduced an LDL cholesterol threshold of 70 mg per deciliter (1.81 mmol per liter) or higher for the addition of nonstatin therapy for secondary prevention in patients with very high cardiovascular risk, and the 2019 European Society of Cardiology–European Atherosclerosis Society guidelines introduced a target LDL cholesterol level of less than 55 mg per deciliter (1.42 mmol per liter), based on the concept that lower is better.2

However, the higher the baseline LDL cholesterol level, the more difficult it is to attain a low LDL cholesterol level. In patients with homozygous familial hypercholesterolemia, untreated LDL cholesterol levels of more than 500 mg per deciliter (12.93 mmol per liter) pose a formidable challenge. Current therapies work through the LDL receptor, and there may be little, if any, residual LDL receptor activity in patients with homozygous familial hypercholesterolemia. Lipoprotein apheresis is a safety net in such patients and in those with severe heterozygous familial hypercholesterolemia. Patients with heterozygous familial hypercholesterolemia, who tend to have untreated LDL cholesterol levels of 190 to 500 mg per deciliter (4.91 to 12.93 mmol per liter), may respond well to current therapies but still not attain sufficiently low LDL cholesterol levels. Other causes of high LDL cholesterol levels, such as polygenic hypercholesterolemia and familial combined hyperlipidemia, could also lead to refractory hypercholesterolemia, especially when drug tolerability limits management.

A new drug target is emerging for the treatment of patients in whom the LDL cholesterol level remains too high despite treatment with existing therapies. Angiopoietin-like 3 (ANGPTL3), an inhibitor of lipoprotein lipase and endothelial lipase, was implicated in lipid metabolism and cardiovascular disease in previous genetic investigations.3,4 Evinacumab, a fully human monoclonal antibody against ANGPTL3, was shown to lower the LDL cholesterol level by 49% in patients with homozygous familial hypercholesterolemia.5

In this issue of the Journal, Rosenson et al. provide more evidence on evinacumab.6 The investigators conducted a randomized, controlled, phase 2 trial involving 272 patients with refractory hypercholesterolemia. Overall, 73% of the patients had heterozygous familial hypercholesterolemia. Overall, 73% of the patients had heterozygous familial hypercholesterolemia, 60% were women, and 90% were White. Refractory hypercholesterolemia was defined as an LDL cholesterol level of 70 mg per deciliter or higher with atherosclerotic cardiovascular disease or a level of 100 mg per deciliter
(2.59 mmol per liter) or higher without atherosclerotic cardiovascular disease, despite background therapy at maximum tolerated doses.

At baseline, nearly all the patients were receiving a PCSK9 inhibitor, 70% were receiving statin therapy (with 46% receiving a high-intensity statin), and 33% were receiving ezetimibe. Yet, the mean LDL cholesterol level at baseline was approximately 150 mg per deciliter (3.88 mmol per liter), which suggests that many patients had untreated levels of 300 to 500 mg per deciliter (7.76 to 12.93 mmol per liter). Three subcutaneous doses of evinacumab (administered weekly or every 2 weeks) and two intravenous doses (administered every 4 weeks) were evaluated for their effect on the primary outcome of the change from baseline in the LDL cholesterol level at 16 weeks. The use of evinacumab reduced the LDL cholesterol level by more than 50% at the maximum dose. Evinacumab also reduced the apolipoprotein B level and all athero-genic lipoprotein levels, and the drug was associated with few high-grade adverse effects.

This trial marks an important milestone in the development of evinacumab. For cases of refractory hypercholesterolemia that are difficult to treat, evinacumab could become an important option for patients and clinicians. A trial of evinacumab that assesses cardiovascular outcomes is warranted and of particular interest, given that the action of evinacumab is independent of the LDL receptor and that the drug has effects on triglycerides and high-density lipoprotein cholesterol levels, in addition to the LDL cholesterol level. For future studies, several learning opportunities emerge from this trial. First, enhanced recruitment strategies are needed to increase the diversity of participants. Second, ezetimibe use could be expanded. Third, assessment of the LDL cholesterol level could be modernized, since the Friedewald equation can overestimate the treatment response by underestimating the LDL cholesterol level at low levels.2,7

As the development of evinacumab progresses and the drug enters clinical practice, fundamental gaps in care require attention. Although approximately 30 million people have familial hypercholesterolemia worldwide, more than 90% of cases remain undiagnosed, and when the diagnosis is made, it is often made late and followed by suboptimal treatment.8,10 Along with expanding the drug armamentarium, we need to build innovative systems of care that can translate evidence into practice in a consistent and cost-effective manner.

The future looks bright for patients and clinicians partnering in lipid management and prevention. An antisense approach to ANGPTL3 is also being pursued, and other promising lipid therapeutics, such as therapies aimed at lipoprotein(a) and apolipoprotein C3, are in the pipeline.7 Furthermore, icosapent ethyl (an agent that lowers levels of triglycerides) and bempedoic acid (an agent that blocks cholesterol synthesis through inhibition of ATP citrate lyase) recently became available, and inclisiran (a small interfering RNA directed at PCSK9) is undergoing regulatory review. A decade ago, the field of lipid therapeutics had its sights set beyond statin therapy. Now, the field is embarking on a frontier beyond PCSK9 monoclonal antibodies, with genetic studies providing a map and patients with familial hypercholesterolemia leading the way.

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