EDITORIALS

Bypassing the LDL Receptor in Familial Hypercholesterolemia

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Several drug options are available for patients with an elevated plasma cholesterol level who are at increased risk for a cardiovascular event. These drugs, which include selective cholesterol-absorption inhibitors and PCSK9 inhibitors as well as statins, effectively lower plasma cholesterol levels in most patients. Unfortunately, these therapeutic options are much less effective in patients with familial hypercholesterolemia, which is a genetic disorder characterized by extremely high levels of low-density lipoprotein (LDL) cholesterol, premature vascular disease, and tendon xanthomas.

Familial hypercholesterolemia is most often caused by a mutation in the LDL receptor, which is responsible for removing LDL from the blood.[1] Statins, cholesterol-absorption inhibitors, and PCSK9 inhibitors lower the plasma cholesterol level by increasing the expression of the LDL receptor on liver cells, thereby stimulating the removal of LDL cholesterol from the blood. Patients with heterozygous familial hypercholesterolemia have plasma cholesterol levels that are two or three times the levels in persons without the disease, but because they have one functional copy of the LDL receptor, they still have some degree of response to standard cholesterol-lowering medications. In contrast, patients with the rare homozygous familial hypercholesterolemia (frequency, 1 per 160,000 to 300,000 persons) are at increased risk for a cardiovascular event before the age of 20 years, and their condition is very difficult to treat. Because of the absence of fully functional LDL receptors, patients with homozygous familial hypercholesterolemia have only a limited response to the existing cholesterol-lowering drugs.[1] Hence, the search continues for new therapies.

In this issue of the *Journal*, Raal and colleagues[2] describe the results of a phase 3 trial in which patients with homozygous familial hypercholesterolemia were treated with evinacumab, a monoclonal antibody against angiopoietin-like 3 (ANGPTL3). This hormone is produced by the liver and inhibits lipoprotein lipase, the enzyme that breaks down plasma triglycerides within the capillaries of muscle and fat tissue. Nearly 20 years ago, investigators determined that mice carrying a mutation in *Angptl3* had decreased plasma levels of triglycerides and total cholesterol.[3] Several years later, large genetic studies showed an association between variations in *ANGPTL3* and plasma triglyceride levels in humans.[4,5] Other studies subsequently showed that loss-of-function mutations in *ANGPTL3* led to exceptionally low plasma levels of triglycerides, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol[6,7] and were associated with a reduced risk of coronary artery disease.[8] Despite ongoing research, it is still unclear how ANGPTL3 deficiency lowers the plasma LDL cholesterol level, but evidence indicates that the effect is independent of LDL-receptor function.[9]

Two strategies targeting ANGPTL3 are currently being pursued. The first strategy involves the inactivation of *ANGPTL3* in the liver with the use of antisense oligonucleotides. The second strategy involves the inactivation of circulating ANGPTL3 protein by monoclonal antibodies. Both approaches have been shown to lower plasma levels of triglycerides and LDL cholesterol in mouse models and in human volun-

teers.[8,10] Notably, ANGPTL3-inactivating human monoclonal antibodies also reduced the size of atherosclerosis lesions in mice with hypercholesterolemia. The effect of ANGPTL3 inactivation on plasma LDL cholesterol levels makes it a very attractive target for patients with homozygous familial hypercholesterolemia because the LDL cholesterol–lowering effect is independent of the LDL receptor.

In their trial, Raal et al. found that evinacumab effectively lowered LDL cholesterol levels in patients with homozygous familial hypercholesterolemia.[2] After 24 weeks of treatment, plasma LDL cholesterol levels were nearly 50% lower in the evinacumab group than in the placebo group. At the same time, plasma HDL cholesterol levels were decreased by 30%. The frequency of adverse events did not differ in the two groups. Although the trial was not designed to assess the effect of evinacumab on cardiovascular risk, the large reduction in LDL cholesterol levels in the evinacumab group would be expected to reduce the risk of such clinical outcomes. This expectation is reinforced by the genetic data.[9]

The results of this trial are great news for patients with homozygous familial hypercholesterolemia and may reduce the need for invasive treatment such as apheresis in some patients. The question then arises as to whether patients without familial hypercholesterolemia who have elevated plasma LDL cholesterol levels may benefit from such therapy. For such patients, evinacumab may become of interest if statins, cholesterol-absorption inhibitors, and PCSK9 inhibitors do not lower LDL cholesterol levels to a sufficient degree or have unacceptable side effects. Since evinacumab also substantially lowered plasma triglyceride levels (a secondary outcome in the trial), the drug may also be useful in patients with familial chylomicronemia syndrome. In this respect, evinacumab differs from other treatments that mainly target LDL cholesterol.

Twenty years after the identification of angiopoietin-like proteins, these hormones have fulfilled their promise as targets for lipid-lowering therapy. Evinacumab is a valuable adjunct to standard cholesterol-lowering therapy in patients with familial hypercholesterolemia and may be clinically useful for a much wider group of patients.

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

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