EDITORIAL COMMENT

Evinacumab Therapy for Homozygous Familial Hypercholesterolemia

Driving Lipoprotein Clearance Via the Road Less Taken*

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Homozygous familial hypercholesterolemia (HoFH) is most frequently attributable to loss of function mutations in both alleles of the low-density lipoprotein receptor (LDLR) gene. The prevalence of HoFH is generally in the 1/250,000 to 300,000 range but can be substantially higher, especially among founder populations such as Afrikaners, French Canadians, and Middle Easterners.[1] This defect leads to impaired binding and clearance of low-density lipoprotein (LDL) particles from the circulation, leading to marked elevations in circulating low-density lipoprotein cholesterol (LDL-C). Genetic variants in the genes for apoprotein B100 (APOB), proprotein convertase subtilisin:kexin type 9, and the LDL receptor adaptor protein 1 can also give rise to phenotypic HoFH due to reduced affinity of apoB for LDLR, increased lysosomal destruction of LDLR, and impaired capacity to sterically align LDL particles within the lipid rafts of hepatocyte cell membranes.

Given the fact that risk for atherosclerotic cardiovascular disease is proportional to both the duration of exposure and the absolute magnitude of elevation in LDL-C, patients with HoFH have marked increases in the prevalence of premature-onset atherosclerotic cardiovascular disease and increased mortality because this genetic disease manifests from the moment of conception and frequently goes undiagnosed.[2] Even when treated, the LDL-C in patients with HoFH can be difficult to reduce to risk-stratified guideline-specified levels, especially when loss of function variants in LDLR are etiologic for the condition. Drugs such as the statins, proprotein convertase subtilisin:kexin type 9 monoclonal antibodies, ezetimibe, bile acid binding resins, and bempedoic acid all provide LDL-C-lowering efficacy, predominantly by upregulating expression of LDLR. However, in patients afflicted with HoFH, the capacity to express LDLR is either nearly completely abolished (null variants) or there may be some residual capacity to express somewhat more functional LDLR (non-null variants). Hence, these therapies have reduced efficacy and frequently have to be used in combinations and/or with LDL apheresis. The microsomal triglyceride transfer protein inhibitor lomitapide reduces LDL-C without increasing hepatic LDLR, but its use has been limited because of concerns over hepatic and intestinal steatosis.[3]

The angiopoietin-like proteins are comprised of a family of 8 secreted glycoproteins (ANGPTL1-8).[4] They are so named because these proteins have high sequence homology with the angiopoietins, which control angiogenesis.[5] In recent years, it has been shown that ANGPTL3, ANGPTL4, and ANGPTL8 participate in the metabolism of triglycerides and triglyceride-enriched lipoproteins (TGRLs) by inhibiting the activity of lipoprotein lipase (LPL).[6,7] The TGRLs include very low-density lipoprotein (VLDL), small VLDL, and the intermediate-density lipoproteins, all of which are precursors to the formation of LDL. In recent years, multiple prospective longitudinal cohorts as well as both genome-wide association

studies and mendelian inheritance studies have shown that the TGRLs participate in atherogenesis.[8] The TGRLs can be cleared by receptors other than LDLR, including the LDL receptor-related protein, the remnant lipoprotein receptor, and the proteoglycan syndecan-1, among others.[9]

LPL is responsible for hydrolyzing the triglyceride mass in lipoproteins and releasing fatty acids, which tissues such as myocardium oxidize for adenosine triphosphate generation. Given its critical role in intermediary metabolism, LPL is an enzyme whose activity is highly regulated. Apoprotein (apo) CIII is an inhibitor, and ApoCII is an activator. The ANGPTLs 3, 4, and 8 also play a role. ANGPTL4 is a potent inhibitor of LPL. When complexed with ANGPTL8, ANGPTL3 is also an inhibitor of LPL, which reduces triglyceride hydrolytic capacity and thereby potentiates increases in serum triglycerides, cholesterol, and TGRLs. ApoA5 binds to the ANGPTL3,8 complex and prevents LPL inhibition.[10] In genome-wide association studies and exome sequencing studies of humans, loss of function variants in *ANGPTL3* are associated with lower serum levels of triglycerides and LDL-C and higher levels of HDL-C. In the DiscoverEHR human genetics study, loss of function variants in ANGPTL3 correlated with a 41% reduction in risk for coronary artery disease.[11] Given such observations, it was hypothesized that neutralizing ANGPTL3 with a monoclonal antibody might provide therapeutic efficacy for reducing LDL-C in the context of HoFH because reduced serum levels of ANGPTL3 correlate with decreased hepatic VLDL secretion and increased conversion of circulating TGRLs to smaller species that could be cleared by lipoprotein receptors other than LDLR.

Evinacumab is a fully human monoclonal antibody directed against ANGPTL3. In a study of humans with homozygous FH evinacumab treatment reduced LDL-C by a mean of 58 ± 18 mg/dL independent of LDLR.[12] In another study of 4 patients with HoFH, evinacumab lowered LDL-C by $59\% \pm 2\%$ and increased intermediate-density lipoprotein apoB and LDL apoB fractional catabolic rates by $616\% \pm 504\%$ and $113\% \pm 14\%$, respectively.[13] In 2 of the patients, VLDL secretion decreased by 64% and 73%, respectively. In the ELIPSE HoFH (Efficacy and Safety of Evinacumab in Patients With Homozygous Familial Hypercholesterolemia) study, 65 patients with HoFH were randomized to either placebo or evinacumab (15 mg/kg of body weight every 4 weeks) therapies for 24 weeks.[14] Evinacumab induced LDL-C reductions compared to placebo in both null-null (<15% LDLR activity) and non-null variants by −43.4% vs +16.2% and by −49.1% vs −3.8%, respectively. Of note, LDL-C reduction was stable over the 6-month follow-up period among patients treated with evinacumab. In addition, evinacumab therapy induced the following mean changes in other metabolic features: absolute change from baseline in LDL-C −134.7 mg/dL, apoB −41.4%, non-HDL-C −49.7%, total cholesterol −47.4%, triglycerides −55%, and ApoCIII −84%. No patient discontinued evinacumab because of an adverse event.

In this issue of *JACC: Advances*, Raal et al[15] report the results of a 24-week open label extension of the ELIPSE HoFH trial to evaluate longer-term efficacy and safety. Results are consistent with the original double-blind treatment period of ELIPSE HoFH with a mean reduction of LDL-C of 46.3% and nearly identical reductions for both null-null and non-null *LDLR* variants, consistent with LDL-C lowering occurring independent of LDLR. Percent reductions in total cholesterol, apoB, and triglycerides were consistent with the original 6-month randomized, placebo-controlled treatment period. Nuclear magnetic resonance spectroscopy confirmed substantial reductions in LDL particle number (−1,008 nmol/L vs −75 nmol/L with placebo), as well as significant reductions in small (−13.8 nmol/L vs −0.9 nmol/L) and medium-sized VLDL particles (−4.0 nmol/L vs no change with placebo). These changes represent 39% and 62% (placebo subtracted) decreases in these VLDLs. At the end of 48 weeks, evinacumab therapy added to ongoing lipid-lowering therapy helped another 22.7% of patients achieve an LDL-C <100 mg/dL and another 23.1% achieve an LDL-C <70 mg/dL. Once again, evinacumab was found to be safe with no toxicity.

Evinacumab therapy is safe and highly efficacious and provides an entirely novel approach to managing the severe elevations in LDL-C in patients afflicted with HoFH. Evinacumab therapy allows clinicians the opportunity to reduce LDL-C via noncanonical pathways, namely, reducing hepatic VLDL secretion and fostering remnant lipoprotein clearance by auxiliary hepatic lipoprotein receptors, thereby reducing dependence on LDLR. This represents a remarkable breakthrough both scientifically and clinically and will hopefully open more novel approaches to lipid lowering and modification.

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