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EDITORIAL COMMENT

Evidence-Based, Mechanistic Approach to the Management of Homozygous Familial Hypercholesterolemia*

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Homozygous familial hypercholesterolemia (HoFH) is a rare autosomal dominant disorder that results from 2 allelic variation in genes encoding the low-density lipoprotein receptor (LDLR) and, less commonly, the LDLR ligand binding site on apolipoprotein B100, the major structural protein of LDL, or gain-of-function mutations in the LDLR-degrading protein proprotein convertase subtilisin kinexin type 9 (PCSK9).[1] Less common causes of HoFH include homozygosity for LDLR adaptor protein 1 (LDLRAP1). Disruption in LDL clearance from the circulation yields marked elevations in LDL cholesterol in the bloodstream that facilitates cholesterol deposition in the skin, tendons, and arteries throughout the body. Depending on the severity of the impaired LDLR function, atherosclerotic cardiovascular disease events have been reported in young children and encompass the spectrum of supravalvular aortic valve stenosis, myocardial infarction, stroke, and peripheral arterial disease.

Early screening for severe hypercholesterolemia in the offspring of patients with heterozygous familial hypercholesterolemia (HeFH), a common disorder affecting 1 gene encoding LDLR or LDLR-regulating mutations, is essential to detect HoFH to forestall the malignant atherosclerosis that causes disability and early death in most of these individuals.[2] Accepted criteria for the diagnosis of HoFH include 1 of the following: 1) confirmed mutations in 2 of the same LDLR regulating pathway genes (true homozygotes); 2) a combination of 2 different mutations in 1 of the disease-causing genes (compound heterozygotes); and 3) untreated total cholesterol of >500 mg/dL in childhood and with both parents having total cholesterol levels of ≥250 mg/dL or cutaneous xanthoma before the age of 10 years.

Lifestyle modification achieved through a low-saturated fat diet, caloric restriction in overweight individuals, and exercise that does not elicit ischemic symptoms in the patient is the cornerstone of treatment.[1] However, pharmacologic and non-pharmacologic approaches are needed to aggressively lower LDL cholesterol in efforts to delay the onset of cardiovascular events that occur early in life and repeatedly throughout the lives of patients with HoFH. Successful treatment strategies require careful evaluation of pharmacologic agents that may be effective in patients with HeFH but ineffective in patients with HoFH because of the severity of the impairment in LDLR activity. Conventional cholesterol-lowering therapies with proven efficacy in the prevention of atherosclerotic cardiovascular events (statins, PCSK9 inhibitors) as well as an approved therapy that is undergoing a phase 3 trial (bempedoic acid) lower LDL cholesterol primarily by up-regulating LDLR activity. In patients with HoFH, the LDL cholesterol–lowering efficacy of statins and PCSK9 inhibitors is about 50% less than that observed in patients with HeFH and may be 0% in patients with null/null mutations in LDLR.[1] In the ODYSSEY (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With

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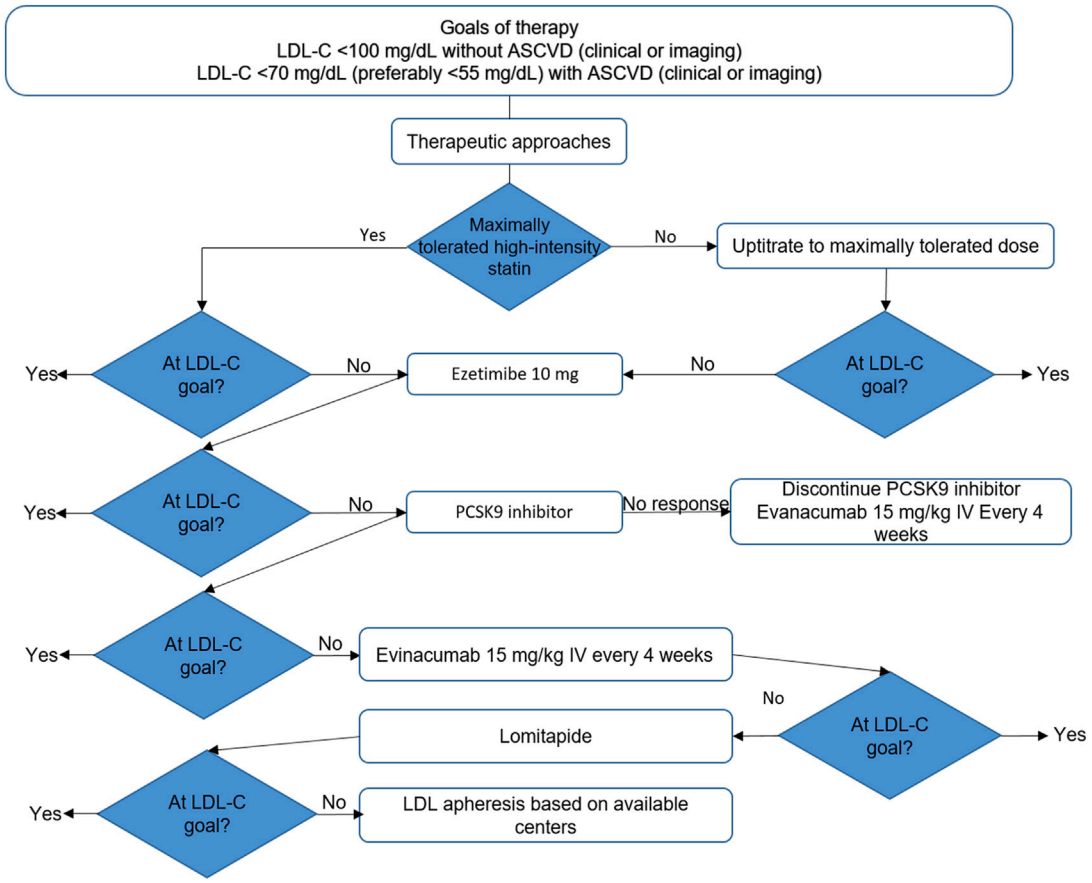
Alirocumab) HoFH trial, LDL cholesterol lowering with alirocumab 150 mg subcutaneously every 14 days lowered LDL cholesterol by an average of 31.0%.[3] Thus, the reduced efficacy of certain cholesterol-lowering therapies requires a structured approach to evaluate efficacy to minimize the use of more and more cholesterol-lowering agents that may have limited efficacy for the patient with HoFH.[1] In addition, the LDL cholesterol-lowering efficacy of bempedoic acid diminishes when combined with statins because of shared pathways in cholesterol biosynthesis.[4] The diminished efficacy of many conventional cholesterol-lowering therapies that lower LDL cholesterol primarily by increasing LDLR activity focused attention on agents that lower LDL cholesterol by LDLR-independent mechanisms.[1]

Non-LDLR-dependent therapies approved for lowering LDL cholesterol in patients with HoFH include lomitapide, a microsomal transferase protein inhibitor; evolocumab, an angiopoietin like 3 protein inhibitor; and LDL apheresis. Lomitapide can effectuate dose-dependent LDL cholesterol lowering. In an open-label, single-arm study of 29 patients with HoFH, therapy with lomitapide (mean dose: 40 mg daily) lowered LDL cholesterol by 50%.[5] The successful use of this agent mandates adherence to a low-saturated fat diet and underscores the critical importance of diet even in the management of HoFH. Mipomersen is rarely used because of the anamnestic site reaction erythema and pain and hepatotoxicity. This agent was approved the U.S. Food and Drug Administration (FDA) on January 29, 2013, but the approval for mipomersen was terminated by the FDA on August 2, 2019, because of a high incidence of flu-like symptoms in 66% of treated patients, including severe flu-like symptoms in 9%. Evinacumab is a fully human monoclonal antibody that lowers LDL cholesterol by primarily disinhibiting endothelial lipase and, to a lesser extent, by unshackling lipoprotein lipase.[1,6] The ELIPSE (Evinacumab Lipid Studies) HoFH trial was a double-blind, placebo-controlled phase 3 trial conducted in patients receiving stable lipid-lowering therapy. At baseline, most patients were treated with a statin (94%), including a high-intensity statin in 77%; ezetimibe was used in 75%, PCSK9 inhibitor in 77%, and lomitapide in 25%.[7] In addition, 34% of patients received LDL apheresis. The mean placebo-corrected reduction in LDL cholesterol from a baseline of 260 mg/dL was -49% (95% CI: -65.0% to -33.1%). The LDL cholesterol-lowering response to evinacumab was the same in patients with no LDLR activity (null-null mutations) or some residual LDLR activity (nonnull-nonnull mutations). A lack of LDL cholesterol-lowering response to evinacumab was observed in only 7% of study participants. When these combinations of cholesterol-lowering agents are proven insufficient, LDL apheresis is an option.[8] An algorithm for the use of these therapies and LDL apheresis in patients with HoFH is depicted in **Figure 1**.[1]

The case by Weintraub et al[9] in this issue of *JACC: Case Reports* discusses a 48-year-old woman with "early onset" coronary artery disease, family history of first-degree relatives with death from atherosclerotic cardiovascular disease before age 40 years, and severe hypercholesterolemia with LDL cholesterol levels of 362 mg/dL on treatment with simvastatin at an unspecified dose and ezetimibe. The skin examination findings were notable for tendon xanthoma affecting the dorsum of the right hand and right Achilles tendon. Genetic testing identified 2 pathogenic mutations in LDLR, supporting a diagnosis of functional HoFH caused by compound heterozygous mutations. At the initial visit, the simvastatin was changed to rosuvastatin (unspecified dose), and ezetimibe was continued. Therapy was initiated with evolocumab at 140 mg/mL subcutaneously every 2 weeks and then changed to the dose equivalent of 420 mg/mL every 4 weeks. Treatment with evolocumab lowered LDL cholesterol by -27%, which is consistent with the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab HoFH trial using alirocumab 150 mg/mL subcutaneously every 2 weeks. Subsequently, the patient was started on bempedoic acid, which has diminishing efficacy when used in combination with a moderate- to high-dose statin. Thus, the data on the rosuvastatin dose are an important consideration. The patient reportedly had no response to evinacumab after an unspecified number of monthly infusions. Although the patient did not consider mipomersen, a treatment no longer available in the United States, there is no discussion concerning the use of lomitapide. Because of the high LDL cholesterol levels on 5 LDL cholesterol-lowering medications, LDL apheresis was initiated. There was a marked 86% reduction in LDL cholesterol; however, the authors do not report whether this was a peak effect of the more conventionally reported trough effect.

Weintraub et al[9] the challenges in achieving effective LDL cholesterol lowering in patients with HoFH. The cholesterol-lowering therapies with established reductions in atherosclerotic cardiovascular events (statins, PCSK9 inhibitors) are most always less effective in these patients because of the severity of the underlying mutations in LDLR. Similar limited efficacy would be expected for

FIGURE 1 Clinical Approach to Patients With Homozygous Familial Hypercholesterolemia



ASCVD = atherosclerotic cardiovascular disease; IV = intravenous; LDL-C = low-density lipoprotein cholesterol.

bempedoic acid in patients with HoFH. The authors make no mention concerning the use of lomitapide but offered an agent that has now been removed from the market because of adverse events. Lomitapide can be effective in lowering LDL cholesterol, but the success of this agent mandates that the patient adhere to a low-fat diet to minimize the common occurrence of gastrointestinal symptoms. Unfortunately, there was no reported response to evinacumab, an agent that was approved by the FDA on February 11, 2021, for treatment of hypercholesterolemia in patients with HoFH. Finally, the patient was offered LDL apheresis. This therapy is effective in HoFH, but this approach has limitations as well, including access that may require an arteriovenous fistula in some patients, infection, and time commitment.

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