Case Report

Treatment of Homozygous Familial Hypercholesterolemia With Evinacumab

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ABSTRACT

Patients with homozygous familial hypercholesterolemia (HoFH) have extremely elevated levels of low-density lipoprotein cholesterol (LDL-C), with premature atherosclerosis and aortic valve disease. Available drug treatments are inadequate, and even with serial apheresis, HoFH patients rarely achieve acceptable LDL-C levels. Evinacumab is a monoclonal antibody against angiopoietin-like protein 3 that lowers LDL-C via a novel receptor-independent mechanism. We describe an Ontario patient with HoFH who for 17 months has been treated with monthly infusions of evinacumab added to pre-existing statin, ezetimibe, and evolocumab therapy. Evinacumab in this HoFH patient was associated with markedly improved LDL-C levels and decreased frequency of apheresis.

RÉSUMÉ

Les patients atteints d'hypercholestérolémie familiale homozygote (HFH) présentent des taux extrêmement élevés de cholestérol à lipoprotéines de faible densité (C-LDL) avec une athérosclérose prématurée et une valvulopathie aortique. Les traitements médicamenteux disponibles sont inadéquats et, même avec un traitement par aphérèses en série, on obtient rarement des taux acceptables de C-LDL chez les patients atteints d'HFH. L'évinacumab, un anticorps monoclonal dirigé contre la protéine 3 de type angiopoïétine, réduit le taux de C-LDL par un nouveau mécanisme indépendant du récepteur. Nous décrivons le cas d'un patient ontarien atteint d'HFH traité par l'évinacumab pendant 17 mois à raison d'une perfusion mensuelle administrée en complément d'un traitement préexistant par une statine, l'ézétimibe et l'évolocumab. L'évinacumab a été associé chez ce patient à une amélioration marquée des taux de C-LDL et à une diminution de la fréquence des aphérèses.

Homozygous familial hypercholesterolemia (HoFH) is an ultra-rare, life-threatening condition that is estimated to affect 1 in 360,000 Canadians.¹ HoFH is characterized by extremely elevated levels of low-density lipoprotein (LDL) cholesterol (C), skin and tendon xanthomas before age 10 years, and high risk of premature atherosclerotic cardiovascular disease (ASCVD).² Most often, HoFH patients have 2 loss-of-function variants in the LDL receptor gene (*LDLR*), and of these, approximately one-third are null mutations.² Untreated HoFH patients may not survive past age 30 years.² Treatment guidelines for HoFH include lifestyle management, use of statins, which are only modestly effective, and other

lipid-lowering drugs, such as inhibitors of proprotein convertase subtilisin kexin type 9 (PCSK9), which are modestly effective only if there is residual LDL receptor activity, and lomitapide, which is somewhat more effective but can pose tolerability issues.² Weekly or biweekly apheresis is the foundation of care.² Although apheresis increases life expectancy, HoFH patients still experience severe ASCVD and aortic valve disease. In addition, HoFH patients rarely attain acceptable LDL-C levels, encounter adverse effects from medications and interventions, and experience decreased quality of life.² Novel treatments are thus needed. Here, we describe the use of evinacumab, a monoclonal antibody against angiopoietin-like protein 3 (ANGPTL3), in the management of an Ontario patient with HoFH.

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Ethics Statement: The patient provided consent and cooperation in the preparation of this report for publication.

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See page 349 for disclosure information.

Case

Our male patient presented with extensive xanthomas at age 14 months, noted by a family physician and referred initially to a dermatologist. HoFH was subsequently diagnosed based on his extreme plasma lipid profile. A skin

Novel Teaching Points

- HoFH is an ultra-rare condition that, if untreated, causes severe premature atherosclerosis.
- Available therapies are modestly effective; serial apheresis is the mainstay of treatment.
- A novel biologic agent, evinacumab, overcomes the impaired lipid metabolism in HoFH.

fibroblast LDL binding assay, performed in the laboratory of Drs. Joseph Goldstein and Michael Brown at the University of Texas Southwestern, revealed the absence of LDL receptor activity (< 2%) and confirmed the diagnosis of HoFH. Several years later, genetic analysis, performed at Robarts Research Institute in London, Ontario, confirmed the molecular diagnosis and revealed that the patient is a compound heterozygote for 2 different mutations in the *LDLR* gene: a deletion of exons 2-6 and a deletion of exons 17-18, located on opposing alleles. DNA analysis also confirmed heterozygous familial hypercholesterolemia (HeFH) in both parents and a sibling, each of whom has only one copy of either mutation. Affected family members had untreated LDL-C levels between 6 and 8 mmol/L, and all have responded well to statins.

When untreated, the patient's total cholesterol ranged from 21 to 23 mmol/L. At age 4 years, the patient started biweekly plasmapheresis at the Toronto Hospital for Sick Children. However, due to technical challenges with plasmapheresis, he often missed treatments, and his condition was not optimally

managed. At age 8 years, he developed symptomatic cardiac ischemia and required triple coronary artery bypass graft surgery with autologous saphenous vein grafts. He remained clinically stable thereafter, and in 2004, at age 18 years, he was referred to the Lipid Genetics Clinic at the London Health Sciences Centre (London, Ontario). Since that time, he has received statin plus ezetimibe, weekly or biweekly plasmapheresis, and lifestyle management. In 2009, at age 23 years, he enrolled in a phase 3 open-label study of lomitapide, but he withdrew after 8 weeks due to intolerable gastrointestinal adverse effects. Since that time, he has declined to resume use of lomitapide.

At age 27 years, he was enrolled in phase 3 randomized placebo-controlled clinical trial of evolocumab, a PCSK9 inhibitor.³ After completing the trial, he continued to receive open-label evolocumab at 420 mg every 2 weeks, administered subcutaneously, which he is still receiving on a compassionate use basis from the manufacturer (Amgen, Mississauga, Ontario). However, evolocumab only minimally changed the patient's lipid profile (Fig. 1), as would be predicted by his genotype. Over time, the patient had ~5% LDL-C reduction with evolocumab, which was about the same magnitude as the effect of statin and ezetimibe. His preference was to continue with all these medications.

Despite these treatments, the patient experienced progression of ASCVD in both graft and native arteries and aortic valve, and progression of aortic root disease, principally aortic stenosis. Initially, his condition was well-compensated. However, as his cardiac health declined, the patient presented with syncope, shortness of breath, and fatigue. Ultimately, at age 32 years, he required a Bentall procedure to replace a severely calcified stenotic aortic valve and

Figure 1. Lipid values and treatment over time. Time course showing pre-apheresis lipid values, with total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) shown. Four main time periods according to treatment are indicated, as follows: **(A)** atorvastatin 80 mg daily, and ezetimibe 10 mg daily, with plasmapheresis once weekly; **(B)** atorvastatin 80 mg daily, ezetimibe 10 mg daily, and evolocumab 420 mg subcutaneously every 4 weeks, with plasmapheresis once every 1 or 2 weeks; **(C)** rosuvastatin 40 mg daily, ezetimibe 10 mg daily, and evolocumab 420 mg subcutaneously every 4 weeks, with LDL apheresis once weekly; and **(D)** rosuvastatin 40 mg daily, ezetimibe 10 mg daily, evolocumab 420 mg subcutaneously every 4 weeks, and evinacumab 1.4 g intravenously every 4 weeks, with LDL apheresis every 4 weeks. Pre-pheresis, post-pheresis, and time-averaged LDL-C levels are shown. The time interval between apheresis treatments is also shown.

atherosclerotic aortic root. At the same time, he underwent a mitral valve replacement and required 2 additional coronary artery bypass grafts. He was then switched from weekly plasmapheresis to LDL apheresis alternating with plasmapheresis weekly (Fig. 1). He continued with evolocumab, rosuvastatin 40 mg daily, and ezetimibe 10 mg daily.

In 2020, at age 34 years, special access to evinacumab was obtained from Health Canada, and the medicine was provided at no cost to the patient from the manufacturer (Regeneron, Tarrytown, NY). Initially, apheresis frequency was maintained at weekly and then biweekly intervals, as he received evinacumab intravenous infusions at 4-week intervals directly after his apheresis. His dose was 1.4 g (15 mg/kg body weight) intravenously every 4 weeks. Evinacumab infusion required an extension of his stay in the apheresis unit by 1 hour. He has been receiving evinacumab for 17 months. After 3 months, the frequency of the patient's LDL apheresis treatments was decreased to every 4 weeks because of the excellent response in LDL-C levels (Fig. 1). Despite reduced frequency of apheresis treatments, the patient's time-averaged LDL-C level has decreased by 33.7%, from 2.41 to 1.60 mmol/L. The patient also reports enhancement in mood and outlook. There have been no self-reported adverse effects since he started taking evinacumab.

Discussion

We present an Ontario patient with severe HoFH and life-threatening cardiovascular complications. Existing LDL-lowering therapies added minimal incremental benefit, although lomitapide was not fully evaluated due to intolerance. The patient has been receiving evinacumab, a monoclonal antibody against ANGPTL3 that has been approved in the US but not in Canada for the past 17 months. This treatment was associated with the following: (i) improvement of time-averaged LDL-C levels, from 2.41 to 1.60 mmol/L, concurrent with (ii) reduction in apheresis frequency; (iii) no reported adverse effects; and (iv) self-reported enhancement in mood and outlook.

ANGPTL3 is a liver-secreted protein with multiple effects on lipid metabolism.⁴ Individuals with inherited *ANGPTL3* deficiency have familial combined hypolipoproteinemia, with no apparent medical complications and reduced risk of ASCVD.⁴ A recent 24-week study of evinacumab in HoFH patients revealed significant reductions in LDL-C levels.⁵ Although the mechanism of ANGPTL3 inhibition and LDL-C level reduction is incompletely understood, it must be partially independent of LDL receptor activity because of its efficacy in HoFH patients.⁴

The mainstay of treatment for HoFH patients has been serial apheresis. This treatment delays mortality, but it is invasive and costly, often negatively impacts patients' quality of life, can sometimes lead to infection or fluid overload, and does not prevent early aortic root disease or coronary atherosclerosis.¹ New treatments are thus needed for HoFH

patients. Evinacumab was recently approved by the US Food and Drug Administration for the primary indication of HoFH. As our observations suggest, evinacumab holds great promise for patients with this rare but potentially devastating condition that has been challenging to manage.

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