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Case Report

Treatment of Homozygous Familial Hypercholesterolemia With ANGPTL3 Inhibitor, Evinacumab

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Abstract

Homozygous familial hypercholesterolemia (HoFH) is an ultra-rare, life-threatening, genetic condition characterized by markedly elevated levels of low-density lipoprotein cholesterol (LDL-C). Standard lipid-lowering therapies minimally reduce LDL-C in these patients, and lifelong serial apheresis is the mainstay of treatment. Evinacumab is a monoclonal antibody against angiopoietin-like protein 3 that lowers LDL-C levels via a novel LDL receptor–independent mechanism, and is US Food and Drug Administration approved for HoFH in the United States. We present a pediatric HoFH patient from Ontario who has been receiving evinacumab through special access from Health Canada. A 17-year-old boy was diagnosed with severe HoFH due to compound heterozygous *LDLR* pathogenic variants. Treatment has included a statin, ezetimibe, and LDL apheresis every 2 weeks, with minimal overall effect on LDL-C levels. He remains asymptomatic from a cardiovascular perspective. At age 16, evinacumab infused intravenously every 4 weeks was added to his treatment. After 12 months, his time-averaged LDL-C decreased by 53.4% from 8.75 mmol/L (338.4 mg/dL) to 4.08 mmol/L (157.8 mg/dL), despite reduced frequency of LDL apheresis from biweekly to monthly. He has experienced no adverse events. Overall, treatment has increased quality of life for him and his family. Evinacumab shows great promise for patients with HoFH, a difficult-to-treat and potentially life-threatening condition.

Key Words: homozygous familial hypercholesterolemia, evinacumab, ANGPTL3 inhibitor

Abbreviations: ANGPTL3, angiopoietin-like protein 3; ASCVD, atherosclerotic cardiovascular disease; FDA, US Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Introduction

Homozygous familial hypercholesterolemia (HoFH) is an ultra-rare, life-threatening, genetic condition characterized by significantly elevated levels of low-density lipoprotein cholesterol (LDL-C) [1]. HoFH affects an estimated 1 in 360 000 North Americans and often leads to atherosclerotic cardiovascular disease (ASCVD) in the first 2 decades of life if untreated [1, 2]. HoFH should be suspected in patients with an LDL-C greater than 10 mmol/L (400 mg/dL), xanthomas starting in childhood, and a family history of heterozygous familial hypercholesterolemia (HeFH) in both parents [2]. HoFH is usually characterized by 2 loss-of-function variants in the *LDLR* gene encoding the LDL receptor [2].

Standard LDL-lowering therapies, such as statins or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, are only modestly effective in HoFH since they depend on patients having residual LDL receptor function [2]. Lomitapide, an oral inhibitor of microsomal triglyceride transfer protein, can be effective in HoFH but is often associated with intolerable side effects, including diarrhea and fatty liver [2]. The current mainstay of treatment in HoFH is serial apheresis, which has demonstrated improved survival, but patients rarely reach guideline-recommended LDL-C levels and may still develop premature ASCVD and aortic valve disease [2]. Given the lack of effective treatment options, novel therapies are needed.

Evinacumab is a new monoclonal antibody against angiopoietin-like protein 3 (ANGPTL3) that lowers LDL-C via a novel LDL receptor independent mechanism (Fig. 1) [3, 4]. It was approved for use in HoFH by the US Food and Drug Administration (FDA) in 2021, but is available in Canada only through clinical trials or government compassionate use programs. There is currently minimal published data on evinacumab in pediatric patients. Here, we describe the second case of HoFH, and first pediatric case, in Ontario, Canada, to be treated with evinacumab.

Case Presentation

Our patient is a 17-year-old boy living in Ontario, Canada. He was initially screened for HoFH in Pakistan at age 2 years given his family history of both parents having HeFH.

Diagnostic Assessment

Based on an extreme plasma lipid profile, he was clinically diagnosed with HoFH. At that time, he was asymptomatic with no physical findings, that is, no xanthomas, and he also had no ASCVD. The patient moved to Canada at age 3 and has since

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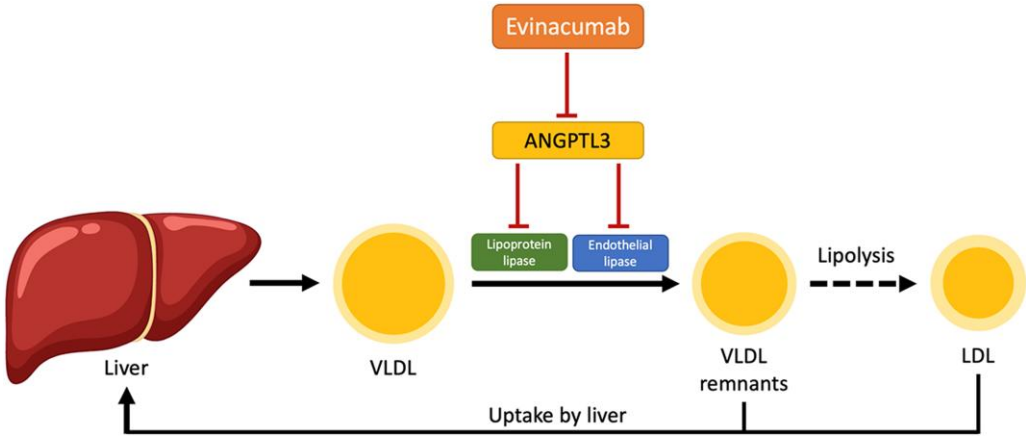

Figure 1. Proposed mechanism of action of evinacumab. Evinacumab inhibits ANGPTL3, which normally inhibits lipoprotein lipase and endothelial lipase [3]. Thus, inhibition of ANGPTL3 by evinacumab increases the activity of lipoprotein lipase and endothelial lipase, which is thought to promote VLDL processing and clearance upstream of LDL formation [3]. ANGPTL3, angiopoietin-like protein 3; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

been followed at the Toronto Hospital for Sick Children. At age 5, he was referred to the Lipid Genetics Clinic at the London Health Sciences Centre (LHSC) (London, Ontario). Genetic analysis performed at Robarts Research Institute in London, Ontario, confirmed the clinical diagnosis and revealed compound heterozygosity for 2 different pathogenic *LDLR* variants: a null variant (p.W-16F > 207X) inherited from his mother and a receptor-defective variant (p.G375S) inherited from his father (Fig. 2). Genetic analysis of his parents and younger brother confirmed that each had HeFH, with a single copy of the respective *LDLR* variants. His parents are each treated with a statin, ezetimibe, and a PCSK9 inhibitor (evolocumab). His younger brother takes a statin and ezetimibe. His father developed symptomatic coronary artery disease at age 46, confirmed angiographically, for which he underwent percutaneous coronary intervention and coronary stenting in 2022. The patient's mother and brother have no cardiovascular complications.

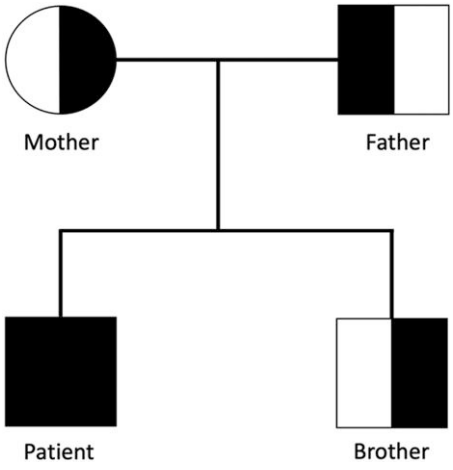

Figure 2. Pedigree of case patient's family. The patient is a compound heterozygote for 2 different *LDLR* variants: p.W-16F > 207X, a null variant, from his mother, and p.G375S, a receptor-defective variant, from his father. His parents and brother each have heterozygous familial hypercholesterolemia; his brother inherited his mother's variant. *LDLR*, low-density lipoprotein receptor gene.

Treatment

After diagnosis, the patient was started on rosuvastatin 20 mg daily, ezetimibe 10 mg daily biweekly plasmapheresis, as well as lifestyle management. Modest improvements in lipid profile were reported with these treatments, although lipid levels within the first year of diagnosis in Pakistan were not systematically recorded. After moving to Canada, he continued on the same treatment regimen initially. He received biweekly plasmapheresis for several years but then developed high sensitization (100% panel-reactive antibodies) and an albumin allergy from numerous blood products and plasma transfusions, which required pretreatment with diphenhydramine [5]. At age 9, he was switched to biweekly LDL apheresis, on which he experienced both better tolerability and improved levels of high-density lipoprotein cholesterol (HDL-C) [5]. However, LDL-C was unchanged on LDL apheresis (Table 1). At age 12, he was trialed on evolocumab, a monoclonal antibody PCSK9 inhibitor, administered subcutaneously every 4 weeks, which was stopped after 6 months because of a minimal approximately 3% LDL-C reduction (see Table 1) [3]. The patient was not eligible for clinical trials involving investigational agents for HoFH.

In 2021, at age 16, special access to evinacumab was obtained for this patient from Health Canada, and doses have been provided to him at no cost from the manufacturer (Regeneron). His dose has been 15 mg/kg of body weight administered intravenously every month, although his absolute dose has been increasing over time as his body weight has increased. His most recent dose was 900 mg. Initially, his LDL apheresis frequency remained at biweekly, but was reduced to monthly after 3 months of evinacumab given the excellent lipid-lowering response (Fig. 3; see Table 1). He now receives evinacumab monthly immediately following his LDL apheresis treatments, which extends his stay in the apheresis unit by 1 hour. He has been receiving evinacumab for more than 1 year.

Outcome and Follow-up

Despite a reduction in the patient's LDL apheresis frequency from biweekly to monthly, his time-averaged LDL-C level decreased by 53.4% from 8.75 mmol/L (338.4 mg/dL) to 4.08 mmol/L (157.8 mg/dL) (see Fig. 3 and Table 1). The patient

Table 1. Pre-apheresis lipid levels in mmol/L (mg/dL in parentheses) at key treatment change time points

	TC	TGs	HDL	LDL	TC:HDL ratio
December 2010—age 5 y	12.6	2.5	0.5	11.0	25.7
On statin, ezetimibe, plasmapheresis	(487.2)	(221.4)	(19.3)	(425.4)	
October 2014—age 9 y	11.2	0.7	0.9	9.9	12.5
Switched to LDL apheresis	(433.1)	(62.0)	(34.8)	(382.8)	
March 2018—age 12 y	13.7	1.9	1.0	11.9	14.1
Started PCSK9 inhibitor, evolocumab	(529.8)	(168.3)	(38.7)	(460.2)	
August 2018—age 12 y Stopped PCSK9 inhibitor, evolocumab	13.2 (510.4)	1.4 (124.0)	1.0 (38.7)	11.6 (448.6)	13.7
October 2021—age 16 y Started ANGPTL3 inhibitor, evinacumab	12.4 (479.5)	1.0 (88.6)	0.8 (30.9)	11.1 (429.2)	16.2
December 2021—age 16 y LDL apheresis frequency reduced to monthly	6.0 (232.0)	0.6 (53.1)	0.7 (27.1)	5.1 (197.2)	9.0
October 2022—age 17 y Most recent lipid profile	6.0 (232.0)	0.5 (44.3)	0.5 (19.3)	5.3 (205.0)	11.5

Abbreviations: ANGPTL3, angiopoietin-like protein 3; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; ratio, ratio of total cholesterol to high-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

also reports improved quality of life, primarily because his apheresis treatments are less frequent, requiring less travel and leaving more free time. He has reported no adverse events since starting evinacumab. He continues on statin plus ezetimibe in addition to monthly evinacumab and LDL apheresis. Throughout the years, he has had good adherence to medication and apheresis, and has remained asymptomatic, with no xanthomas or known ASCVD or aortic disease. In 2022, he had a normal nuclear medicine cardiac stress test and echocardiogram.

Discussion

We report a 17-year-old boy with HoFH living in Ontario, Canada. After experiencing only modest reductions in his LDL-C levels with existing LDL-lowering therapies, he was started on evinacumab; he is the first pediatric patient in Canada to receive evinacumab on a special access basis. After 12 months of treatment, he had a 53.4% reduction in time-averaged LDL-C levels, a reduction in the frequency of LDL apheresis from biweekly to monthly, self-reported improved quality of life, and no adverse events. After lengthening his apheresis treatment interval to monthly after starting evinacumab, his HDL-C levels returned to his baseline levels from 2010, but this is unlikely to be clinically significant given his more significant LDL-C reduction rendering the HDL-C change relatively inconsequential. He has remained asymptomatic from the disease, and recently underwent cardiac testing showing no evidence of atherosclerotic or structural heart disease. The first HoFH patient in Canada to receive special access to evinacumab has previously been reported [6]. Prior to starting evinacumab, that patient had substantial atherosclerotic complications from his disease requiring coronary artery bypass grafts and a Bentall procedure (aortic root and valve replacement) [6]. At age 34 years, he was started on evinacumab, and after 17 months of treatment, demonstrated a 33.7% reduction in time-averaged LDL-C, reduced apheresis frequency, improved quality of life and no adverse events [6].

Standard lipid-lowering therapies are only modestly effective at lowering LDL-C in HoFH patients, and do not lower LDL-C to guideline-recommended levels [2]. Statins and PCSK9 inhibitors act by upregulating LDL receptor expression, so they can be effective only in patients with residual LDL receptor function [2]. Lomitapide does not rely on functional receptors and can be effective in HoFH, but is often not tolerated because of gastrointestinal side effects [2]. Serial apheresis is the mainstay of therapy for patients with HoFH and has been shown to reduce mortality, but is invasive, costly, and often negatively affects quality of life [1].

Evinacumab is a fully human monoclonal antibody that inhibits ANGPTL3, a liver-secreted protein with a key role in lipid metabolism [3, 4]. ANGPTL3 normally inhibits lipoprotein lipase and endothelial lipase, which promote very-low-density lipoprotein processing and clearance upstream of LDL particle formation (see Fig. 1) [3]. Therefore, evinacumab decreases LDL-C levels via an LDL receptor–independent mechanism [3]. Genetic studies of *ANGPTL3* loss-of-function variants have demonstrated reductions in both LDL-C levels and incidence of ASCVD [4]. A phase 3, randomized, placebo-controlled trial of patients with HoFH demonstrated a 47% reduction in LDL-C after 24 weeks of treatment with evinacumab [7]. Evinacumab is generally well tolerated, but some potential side effects include influenza-like symptoms and infusion-site pruritis [7]. Evinacumab was approved for use in those with HoFH aged 12 years and older by the US FDA in 2021 and recently received US FDA approval in young children with HoFH aged 5 to 11 years in March 2023 [https://www.biopharminternational.com/view/fda-approves-evkeeza-for-young-children-with-ultra-rare-form-of-high-cholesterol]. However, it is available in Canada so far only through clinical trials or special access programs. Our case indicates that evinacumab shows great promise as an effective treatment option for HoFH, a difficult-to-treat and potentially life-threatening condition.

Learning Points

- HoFH is an ultra-rare, life-threatening condition characterized by extremely elevated LDL-C levels that can lead to premature ASCVD if left untreated.

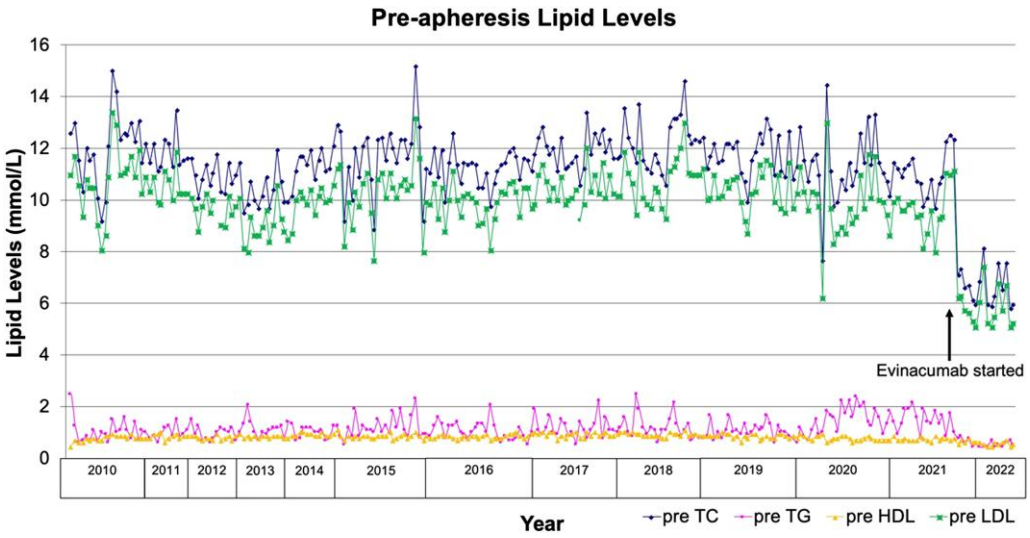

Figure 3. Pre-apheresis lipid levels over time. After evinacumab was started in October 2021, there was a clear reduction in total and LDL cholesterol and triglycerides. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

- Standard lipid-lowering therapies are only modestly effective at lowering lipid levels in these patients and the mainstay of treatment is serial apheresis.
- Evinacumab, an ANGPTL3 inhibitor, is a novel therapy for HoFH approved in the United States, but available in Canada only through clinical trials or compassionate use programs.
- This case demonstrates, after 1 year of treatment with evinacumab, a greater than 50% reduction in LDL-C levels, showing great promise as an effective treatment option for HoFH.

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Contributors

All authors made individual contributions to authorship. I.S. was responsible for data collection and analysis, and manuscript preparation. B.W.M. and R.A.H. were involved in the diagnosis and management of this patient. R.A.H. was responsible for manuscript submission. All authors reviewed and approved the final draft.

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Disclosures

R.A.H. reports receiving consulting fees from Acasti, Akcea/Ionis, Amgen, Amryt, Arrowhead, HLS Therapeutics, Medison, Novartis, Pfizer, Regeneron, Sanofi, and Ultragenyx. B.W.M. reports receiving consulting fees from Amryt, Chiesi, Esperion, Janssen, and Ultragenyx. I.S. has nothing to disclose.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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