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Brief Communication

Safety and effectiveness of evinacumab in an infant with homozygous familial hypercholesterolemia: A new renaissance for the very young?

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The rare homozygous form of familial hypercholesterolemia (HoFH) is characterized by extremely high low-density lipoprotein (LDL) cholesterol levels, typically exceeding 13 mmol/L (500 mg/dL), and a variable phenotype that may include marked premature atherosclerotic cardiovascular disease. HoFH with null-null LDL receptor mutations can be highly resistant to standard pharmacological therapies. The standard of care treatment option is lipoprotein apheresis (LA). However, LA is not commonly available, is technically demanding, and is relatively invasive and arduous for very young patients. Here we report effective lowering of the LDL cholesterol in a 13-month-old child with HoFH treated with evinacumab, initially at a low dose (7.5 mg/kg), later increased to 15 mg/kg/28 days. The decision was made after the failure of standard drug therapies in a sibling with the same null-null mutation in the LDL receptor, submitted to liver transplantation, who had severe complications. The treatment with evinacumab was safe and effective; LDL cholesterol, triglycerides, and apolipoprotein B concentrations all decreased by over 80%. Our findings suggest that evinacumab is a safe and effective option for treating very young patients with HoFH who do not respond to conventional therapies.

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Introduction

Familial hypercholesterolemia (FH) is the most common monogenic disorder causing premature atherosclerotic cardiovascular disease (ACVD).[1] Homozygous FH (HoFH) is rare, affecting one person per 160,000 to 200,000 in Europe.[1,2] It is characterized by extremely high low-density lipoprotein cholesterol (LDL-C) levels, typically exceeding 13 mmol/L (500 mg/dL) from birth throughout life, a heterogeneous phenotype, and marked premature ACVD.[3] The phenotype may include xanthomas in early childhood, but HoFH is clinically silent in most cases, contributing to delays in diagnosis.[4,5] Fatal atherosclerotic cardiovascular events have been reported in children in the first decade of life.[2]

Patients with homozygous *LDLR* mutations can be highly resistant to standard pharmacological therapies, such as statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which act by up-regulating *LDLR* expression.[2,6,7] In addition, while drugs previously reserved for adults are becoming more accessible for pediatric use, treatment options remain limited. Lipoprotein apheresis (LA) is a safe and effective therapeutic strategy, but its application can be technically challenging, especially in very young children, due to the limited access to centers specializing in the invasive procedure, smaller extracorporeal blood volume, the difficulty of venous access, and other age-related challenges. Nevertheless, LA may be feasible, even in very young children, in centers with extensive experience in extracorporeal therapeutic techniques.[8-10]

Evinacumab is a monoclonal antibody against angiopoietin-like protein (ANGPTL) that reduces LDL-C with an LDLR-independent mechanism.[11] It has been shown to be effective in treating HoFH in adults and children,[12-14] but it has never been tested in very young children.

Clinical history of 2 siblings with HoFH

We describe the clinical history of 2 siblings affected by HoFH from nonconsanguineous parents. The family pedigree is shown in Figure 1. The description highlights the differences between the 2 different therapeutic approaches and shows the effectiveness of evinacumab therapy in the youngest sibling.

Patient 1, female, was born in Kosovo in September 2019. Diffuse cutaneous xanthomas appeared at 6 months of age. A hospitalization at 8 months for pneumonia revealed severe hypercholesterolemia, with an LDL-C of 14.87 mmol/L (575 mg/dL). Electrocardiography, supra-aortic trunk (SAT) echo-Doppler, and echocardiogram were negative. The genetic analysis identified HoFH (*LDLR* homozygous mutation c.1646G>*A* p.(Gly549Asp) in exon 11). In June 2020, she started atorvastatin 10 mg/d + ezetimibe 10 mg/d. She was transferred to Bozen in Italy in August 2020, and in October she was referred to our clinic for specialist consultation. The family history of hypercholesterolemia was positive: mother LDL-C 6.3 mmol/L (244 mg/dL), father LDL-C 7.6 mmol/L (293 mg/dL), and triglycerides (TG) 4.3 mmol/L (382 mg/dL). The genetic analysis revealed a heterozygous mutation in *LDLR* (c.1646G>*A*) in both parents. No family history of early ACVD was reported.

The dietitian provided the family with nutritional information according to the Cardiovascular Health Integrated Lifestyle Diet Pediatric Guidelines.[4] Over the next 3 months, we tried to increase the off-label statin therapy (up to rosuvastatin 20 mg/d + ezetimibe 10 mg/d), which was well tolerated (no symptoms, negative hepatic transaminases, and creatine kinase) but with no variation in lipid profile. Cardiological examination, resting electrocardiography, and echocardiogram were negative. At the same time as being referred for evaluation to our clinic, the Endocrinologist scheduled a medical consultation at the Transplant Center of the Bergamo Hospital, where liver transplantation was proposed. In April 2021, she received a liver transplant. Due to post-transplant complications (slow neurological recovery, granulocytic cholangitis associated with ischemia-reperfusion injury, Roux's loop bleeding), she was hospitalized for 4 months. During the following years, further hospitalizations were necessary. Her lipid profile has completely normalized, and the xanthomatous lesions have improved. She is continuing follow-up and immunosuppressive therapy.

Patient 2, male, was born in Italy in April 2022. Owing to family history, screening examinations were performed in September 2022, with a first finding of severe hypercholesterolemia: total-C 22.9 mmol/L (884 mg/dL), LDL-C 17.9 mmol/L (692 mg/dL), TG 5.2 mmol/L (459 mg/dL). He came to our attention in December 2022. The clinical exam was normal. Genetic analysis confirmed HoFH (*LDLR*

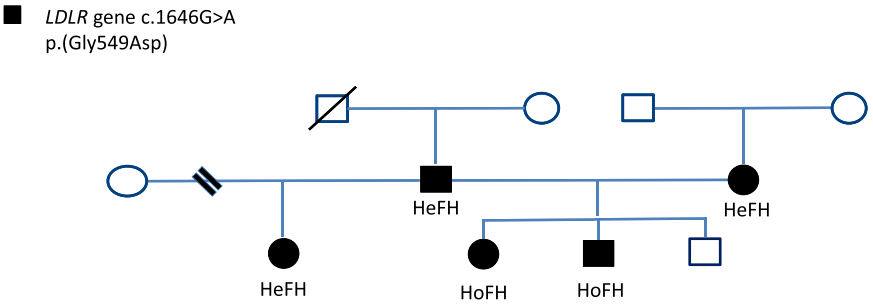

Figure 1. Family pedigree.
HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; *LDLR*, gene encoding low-density lipoprotein receptor.

Table 1. Lipid profile during evinacumab treatment of patient 2, the male sibling of patient 1.

Date	Total-C (mmol/L / mg/dL)	LDL-C (mmol/L / mg/dL)	TG (mmol/L / mg/dL)	HDL-C (mmol/L / mg/dL)	Non-HDL-C (mmol/L / mg/dL)	AST (U/L)	ALT (U/L)	GGT (U/L)
May 2023	33.7 / 1300	32.8 / 1268	3.5 / 307	0.8 / 32	32.8 / 1268	56	26	11
Jun 2023	18.4 / 709	16.4 / 632	3.3 / 292	0.5 / 19	17.9 / 690	37	22	13
July 2023	10.3 / 388	9.1 / 351	1.2 / 102	0.7 / 28	9.6 / 371	47	23	17
Aug 2023	9.8 / 379	8.7 / 335	1.0 / 86	0.6 / 25	9.2 / 354	45	19	14
Sep 2023	10.1 / 389	8.9 / 342	0.8 / 69	0.8 / 31	9.3 / 358	hemolytic	32	5
Oct 2023	7.4 / 286	6.4 / 246	0.9 / 76	0.6 / 25	6.8 / 261	hemolytic	26	11
Nov 2023	7.6 / 293	6.7 / 257	0.7 / 61	0.6 / 23	7.0 / 270	46	18	11
Dec 2023	8.1 / 313	7.1 / 276	0.6 / 52	0.7 / 26	7.4 / 287	52	30	11
Jan 2024	6.5 / 251	5.8 / 223	0.4 / 37	0.5 / 21	6.0 / 230	35	22	10

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; Total-C, total cholesterol; U, units.

homozygous mutation c.1646G>*A* p.(Gly549Asp) in exon 11). Echocardiogram, resting electrocardiography, and SAT echo-Doppler were regular. A coronary computed tomography angiography was performed, and no coronary anomalies or calcifications of the aortic root were found.

Considering the lack of response to the high-dose treatment with statin and ezetimibe of the sister with the same *LDLR* null-null mutation, the nonavailability of an LA center with expertise in pediatric extracorporeal treatment close to our hospital, and the inappropriate age for lomitapide therapy, we decided on the compassionate use of evinacumab. With the consent of both parents and after approval by the local ethics committee (protocol number 7079, November 2, 2022), we started evinacumab therapy in May 2023. To better monitor any adverse reactions and possible side effects, the first 4 administrations of the drug were carried out in an in-patient regimen. The subsequent infusions were carried out in a daytime hospital setting, with observation for approximately 6 hours after administration. Evinacumab was administered via intravenous infusion over 60 minutes once monthly. We calculated the first administration dose at half the 15 mg/kg therapeutic dose indicated for adults, to evaluate the tolerability of the drug. A stringent follow-up with clinical and biochemical assessment was performed with no evidence of adverse events. From the second dose, the drug was administered at the full dose (15 mg/kg).

A complete lipid profile was performed before treatment: total-C 33.6 mmol/L (1300 mg/dL), LDL-C 22.6 mmol/L (872 mg/dL), TG 3.5 mmol/L (307 mg/dL), apolipoprotein B (ApoB) 0.0134 mmol/L (6.88 g/L), lipoprotein(a) [(Lpa])<0.2 g/L (<200 mg/L).

There was a significant reduction in LDL-C, with already a decrease of 50% from baseline after the first administration at half the dose and a maximum LDL-C decrease of 82% after the first 8 infusions. The TG concentration reduced from 3.5 mmol/L (307 mg/dL) at baseline to 0.4 mmol/L (37 mg/dL), a decrease of 88%. No significant changes were observed in high-density lipoprotein (HDL)-C levels. ApoB concentration reduced from 0.134 mmol/L (6.88 g/L) to 0.0025 mmol/L (1.27 g/L) (a decrease of 82%). Table 1 and Figure 2 show the trend of the lipid profile during the treatment period. Follow-up hepatic screening exams showed no alterations. Cardiovascular follow-up exams (echocardiogram, electrocardiography) repeated 1 year after the first screening were regular.

After the first 8 months of therapy, evinacumab remained well-tolerated throughout the treatment period. No injection-site reactions or signs and symptoms of possible adverse effects were observed. The treatment is continuing.

Discussion

We describe the effectiveness of evinacumab in lowering LDL-C and TG in a 13-month-old child with HoFH. To our knowledge, this is the first case of evinacumab therapy in an infant with HoFH carrying a null-null mutation. Evinacumab rapidly and substantially reduced LDL-C levels and TG and ApoB concentrations also decreased by over 80% without significantly changing HDL-C levels. The treatment was well tolerated throughout, and follow-up cardiovascular examinations were normal.

The *LDLR* gene mutation on exon 11 c.1646G>*A* p.(Gly549Asp) was previously described in Italy in the largest cluster in Southern Italy in terms of the number of families and includes 78 families, 3 homozygotes, 4 compound heterozygotes, and 163 heterozygotes. The mutation has also been described in Greek patients, with a frequency ranging from 23% to 30%. The geographical distribution corresponds to the areas colonized by the Greeks from the VIII to the IV century B.C. (Magna Graecia).[15] A homozygous patient is described in Spain,[16] and a compound heterozygous patient is described in the Kosovo area.[3] The mutation is characterized by a residual function of LDLR measured on fibroblasts of <2% and the calculated severity score is intermediate (0.612).[17]

The severity of the phenotype determines the need to start therapy as early as possible, and early identification of the genetic mutation can guide clinicians on the most appropriate therapeutic approach.[18] The results for our patient are con-

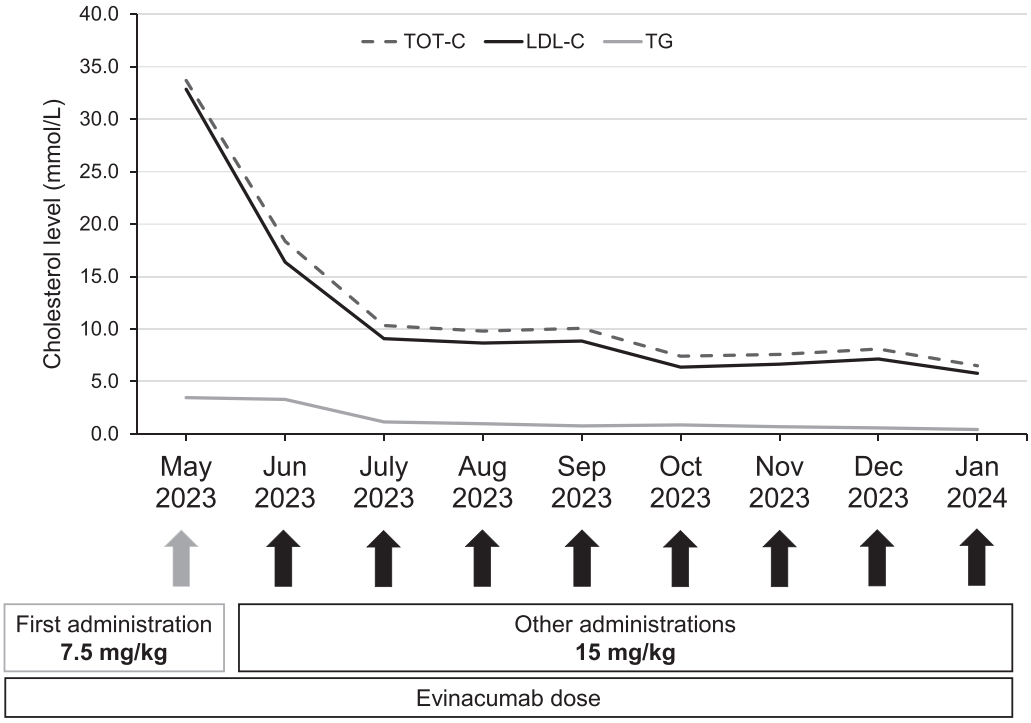

Figure 2. Trend in lipid profile during evinacumab treatment (Patient 2).
LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TOT-C, total cholesterol.

sistent with previous studies showing the efficacy and safety of evinacumab HoFH patients aged 12 to 16 years.[13,19] Stefanutti et al.[19] described how evinacumab was able to reduce the plasma lipid and lipoprotein levels in 7 patients during 2 months of follow-up: LDL-C −46.8%, TG −44.5%, non-HDL-C −46.6%, and ApoB −33.8%. The potent LDL-lowering effect of evinacumab appears independent of the degree of LDL receptor activity, the putative mechanism of LDL reduction considered to be due to increased hepatic clearance of very-low-density lipoprotein with a decreasein the production of LDL-apoB.[19] Evinacumab reduced the total apolipoprotein concentration of apolipoprotein B-100 in our patient.

Unfortunately, no data regarding lipoprotein (mainly Lp(a) concentration) are available, since our laboratory does not titrate Lp(a) levels under 0.2 g/L. This represents a limitation. However, previous studies have highlighted how evinacumab treatment lowered both the apolipoprotein and lipoprotein concentrations.[19] The main strength of this report is that it describes the youngest patient with HoFH effectively treated with evinacumab, not associated with other cholesterol-lowering treatments.

Patients with HoFH have an extremely reduced life expectancy, and early diagnosis and effective therapy can guarantee them decades of healthy life.[2] When a diagnosis is confirmed, a very aggressive cholesterol-lowering therapy should be started as soon as possible.[2] Although a healthy lifestyle and the combination of statins, ezetimibe, evolocumab, and LA are the cornerstones of managing FH in childhood, the first-line drug therapy can be completely ineffective in HoFH, making treatment, especially in pediatric patients, a challenge. The beneficial effects of evinacumab in safely and effectively treating HoFH and improving patients' quality of life are becoming recognized, particularly in limiting the need for long-term LA and onerous therapeutic invasive strategy, such as liver transplantation with chronic immunosuppressive treatment.[19,20] The potential benefits of evinacumab, both in terms of safety and efficacy and concerning the quality of life in patients with HoFH, have been highlighted in recent publications.[19,20]

Although LA is a highly effective treatment, it is not always feasible in very young children, as already discussed, and also due to the possible distance of specialized centers from the patient's home. Liver transplantation is a radical and highly invasive approach and, as indicated by the guidelines, should be the last choice of treatment. Due to the possible serious complications and the need for chronic immunosuppressive therapy, this procedure could also negatively affect the patient's quality of life, as occurred in his sister. Pharmacological therapeutic options constantly evolve, and approaches such as evinacumab could represent safe, effective, and minimally invasive treatment options.

Treatment options are currently limited for pediatric patients with severe FH. Ensuring a healthy lifestyle, with the need for repeated blood sampling, drug administration, and invasive procedures, is challenging and requires special efforts from parents and shared decision-making with healthcare providers. The effectiveness of newly emerging drugs with good tolerability and minimal invasiveness represents an excellent opportunity for improving patients' life ex-

pectancy and quality of life. As pharmacological therapeutic options evolve, evinacumab could represent such an effective and minimally invasive treatment option.

Implications for clinical practice

Our findings suggest that evinacumab is safe and effective for very young HoFH patients unresponsive to conventional therapies. Further research is needed to assess its use in children under 4, either alongside or as an alternative to standard drug treatments and LA.

CRediT authorship contribution statement

Elena Fornari: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Claudia Stefanutti:** Writing – review & editing. **Valentina Mancioppi:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Gerald F. Watts:** Writing – review & editing. **Livia Pisciotta:** Writing – review & editing, Writing – original draft. **Anita Morandi:** Writing – review & editing. **Claudio Maffeis:** Writing – review & editing.

Ethical approval

The work was carried out with the consent of both parents and with the approval of the local ethics committee (protocol number 7079, November 2, 2022).

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Declaration of competing interest

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