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Brief Communication

LDL-C target achievement after adding evinacumab in 2 patients with autosomal recessive hypercholesterolemia

Giuliana Germana Mombelli, MD*; Chiara Pavanello, PhD; Francesco Vicari, MD; Chiara Moschetti, MSc; Antonia Alberti, MD; Laura Calabresi, PhD; Cesare Riccardo Sirtori, MD, PhD**

Dyslipidemia Center, Niguarda Hospital, Milan, Italy (Mombelli, Dr Pavanello, Vicari, Alberti, and Dr Sirtori); E. Grossi Paoletti Center, Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan, Milan, Italy (Dr Pavanello, Moschetti, and Dr Calabresi)

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Autosomal recessive hypercholesterolemia;
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BACKGROUND: Autosomal recessive hypercholesterolemia (ARH) is a rare form of genetic hypercholesterolemia consequent to pathogenic variants in the low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*) gene, coding for a protein responsible for moving LDL-receptor (LDL-R) to its site of activity. ARH is characterized by very high levels of LDL cholesterol (LDL-C), leading to aggressive and frequently premature atherosclerotic cardiovascular disease (ASCVD). Lowering of LDL-C is the main target of treatment; however, classical lipid-lowering agents, for example, statins, frequently have a modest response, in view of their selective LDL-R–raising activity.

OBJECTIVE: Among newer agents with an LDL-R–independent mechanism, evinacumab has been shown to be effective in homozygous familial hypercholesterolemia, but few data are available in *LDLRAP1* variant carriers.

METHODS: We here report 2 cases of this extremely rare form of familial hypercholesterolemia with a surprising response to evinacumab. Evinacumab was added to maximally tolerated background therapy.

RESULTS: In the first patient, who had severe ASCVD and a prior inadequate response to statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and lomitapide, evinacumab reduced time-averaged LDL-C by 82% (from 549 to 62 mg/dL). In the second patient, evinacumab achieved a sustained 73.8% LDL-C reduction, maintaining levels < 55 mg/dL and allowing discontinuation of the PCSK9 inhibitor.

CONCLUSION: These cases demonstrate a marked and clinically meaningful LDL-C–lowering effect of evinacumab in ARH, supporting its use as an effective LDL-R–independent therapeutic option.

* Corresponding author at: Dyslipidemia Center, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy.
** Corresponding author at: E. Grossi Paoletti Center, Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan, Via Balzaretti 9, 20133 Milan, Italy.
E-mail addresses: giuliana.mombelli@ospedaleniguarda.it (G.G. Mombelli), chiara.pavanello@unimi.it (C. Pavanello).
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Introduction

The global burden of dyslipidemias, in terms of prevalence and related mortality, has increased substantially over the past 3 decades, with hypercholesterolemia being the most prevalent form. Elevated low-density lipoprotein cholesterol (LDL-C) concentrations are recognized as a primary causal factor for the onset of atherosclerotic cardiovascular disease (ASCVD) in both developed and developing regions of the world.[1]

Familial hypercholesterolemia (FH) develops as a result of variants in genes associated with the LDL-receptor (LDL-R) pathway, including *LDLR, proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (APOB)*, and LDL receptor adaptor protein 1 (*LDLRAP1*).[2] Patients with heterozygous FH carry a pathogenic variant in a single allele, resulting in LDL-C levels approximately twice the normal mean. Individuals with homozygous FH (HoFH) exhibit LDL-C levels 4 times higher than those of non-carriers.[2] In these, ASCVD develops earlier and, if left untreated, may result in the onset of severe forms within the first 2 decades of life.

Autosomal recessive hypercholesterolemia (ARH) is a rare form of FH caused by pathogenic variants in the *LDLRAP1* gene, which encodes an intracellular adaptor protein that facilitates LDL-R endocytosis in hepatocytes and is essential for LDL-R functionality. ARH is characterized by markedly elevated LDL-C levels, leading to aggressive and premature ASCVD. However, in the absence of a functional LDL-R, as in ARH, the response to conventional lipid-lowering therapies, including statins, ezetimibe, and PCSK9 inhibitors, is only modest.[3] Better results may be achieved with lomitapide, which acts independently of the LDL-R pathway.[4,5] Most frequently, carriers of severe *LDLRAP1* variants need to undergo serial lipoprotein apheresis (LA), a procedure that involves the removal of atherogenic lipoproteins from the circulation.[6]

Among the novel classes of cholesterol-lowering medications for this ultrarare form of hypercholesterolemia, evinacumab is a fully human monoclonal antibody that lowers LDL-C via a novel LDL-R–independent mechanism.[7] Evinacumab inhibits angiopoietin-like protein 3, an endogenous inhibitor of lipoprotein lipase and endothelial lipase. By raising the activity of both enzymes involved in the hydrolysis of triglycerides and phospholipids in the very low-density lipoproteins (VLDL), evinacumab promotes the formation of lipid-depleted VLDL remnant particles, which are more rapidly cleared from the circulation, thus reducing the pool of LDL precursors. As a result, LDL-C levels decrease independent of residual LDL-R functionality.

We here report 2 cases of severe hypercholesterolemia, who are carriers of biallelic pathogenic variants in *LDLRAP1*, showing an impressive response to evinacumab, far higher than that reported in other series of patients with FH.

Case presentations

First case

A 60-year-old man of Sardinian origin was diagnosed with ARH, with genetic confirmation at the age of 47. Molecular analysis revealed that he was homozygous for the *LDLRAP1* gene variant (NM_015627.3): c.431dup (p.His144Glnfs*27). This ultrarare variant causes a frameshift at the protein level, leading to the introduction of a premature stop codon. In 2024, genetic testing was repeated at our institution using next-generation sequencing (NGS), which confirmed the initial findings. The patient was found to be a carrier of the APOE ε3/ε3 genotype. The earliest clinical sign, at age 8, was the appearance of tendon xanthomas, still evident at the time of evaluation (Fig 1). Untreated lipid values (total cholesterol [TC] 667 mg/dL, triglycerides [TGs] 62 mg/dL, high-density lipoprotein cholesterol [HDL-C] 47 mg/dL, and LDL-C 608 mg/dL) were documented from the age of 13. During adolescence, he was treated with cholestyramine at varying dosages. At the age of 23, after 4 years of therapy with cholestyramine 16 g and simvastatin 20 mg, LDL-C levels remained above 400 mg/dL. Probucol 500 mg twice a day was then introduced, resulting in a significant improvement (Table).

He presented to our Lipid Clinic at age 27 as a smoker, with no family history of hyperlipidemia or premature ASCVD. Direct adsorption LA was subsequently initiated on a twice-weekly schedule. He continued treatment with cholestyramine 8 g, atorvastatin 40 mg, and probucol 1 g for 7 years, achieving an incomplete reduction in LDL-C (mean 179 mg/dL). When ezetimibe became available in clinical practice, it was added to the regimen but yielded no additional benefit. At the age of 42, a carotid ultrasound followed by angiography revealed severe stenosis of the left internal carotid artery, treated by endarterectomy. In 2008,

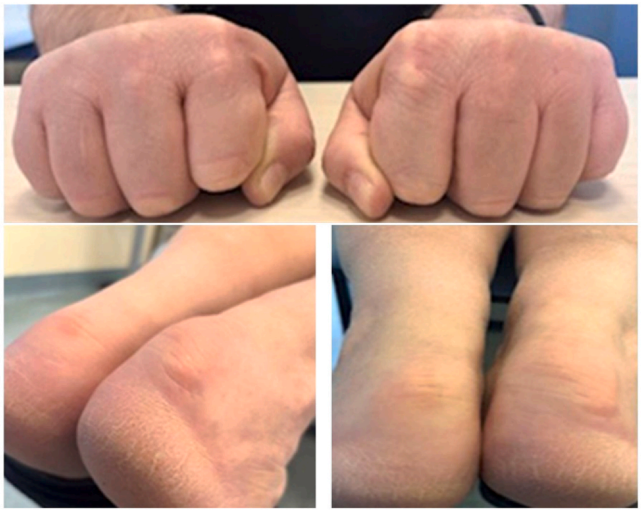


Figure 1. Metacarpal and Achilles tendon xanthomas of patient 1.

Table. Evolution of the lipid profile according to treatment history in the 2 cases.

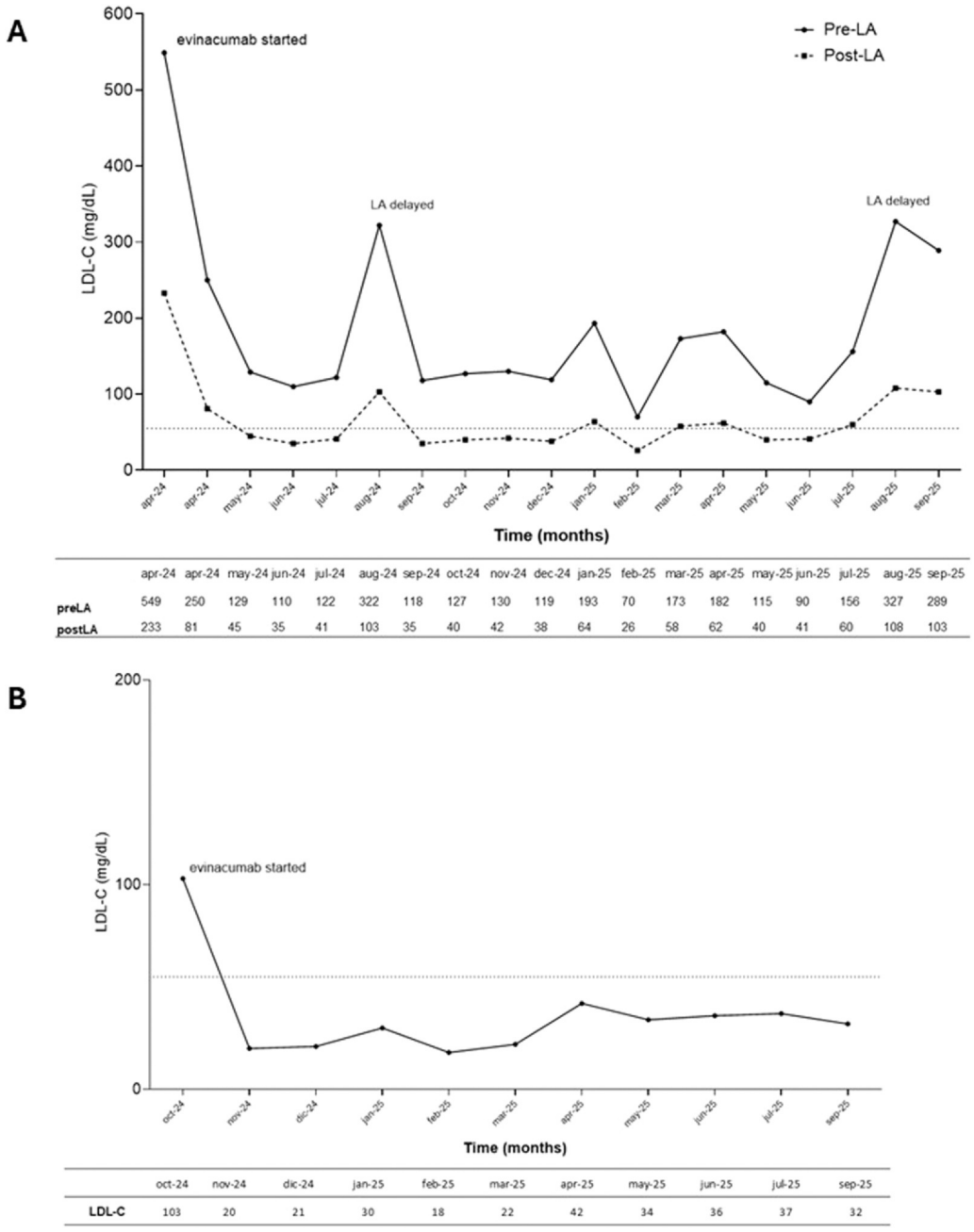
Age (y)	LDL-C (mg/dL)	Treatment
Case 1		
8	608	No treatment
13-22	> 450	Cholestyramine 8-16 g
23-26	> 400	Cholestyramine 16 g + simvastatin 20 mg
27-30	179	Cholestyramine 8 g + atorvastatin 40 mg + probucol 1 g
30-44	190	Cholestyramine 8 g + atorvastatin 40 mg + probucol 1 g + LA
45-46	194	Rosuvastatin 30 mg + ezetimibe 10 mg + fenofibrate 145 mg + LA
46-47	44	Rosuvastatin 30 mg + ezetimibe 10 mg + fenofibrate 145 mg + LA + lomitapide 5-20 mg
48-52	220	Rosuvastatin 30 mg + ezetimibe 10 mg + fenofibrate 145 mg + LA
53-55	200	Rosuvastatin 30 mg + ezetimibe 10 mg + fenofibrate 145 mg + LA + evolocumab 140-420 mg/Q2W
55-56	78	Rosuvastatin 30 mg + ezetimibe 10 mg + fenofibrate 145 mg + lomitapide 5 mg
56-58	229	Rosuvastatin 30 mg + ezetimibe 10 mg + fenofibrate 145 mg + LA
59-60	70 (pre-LA) 26 (post-LA)[a]	Rosuvastatin 30 mg + ezetimibe 10 mg + LA + evinacumab Q4W
Case 2		
9	> 650	No treatment
10-15	> 400	LA Q2W
15-24	> 250	Atorvastatin 40-60 mg + LA Q2W or Q8W
25-34	< 100	Simvastatin 40 mg + ezetimibe 10 mg + LA Q2W
35-41	90-100	Rosuvastatin 40 mg + ezetimibe 10 mg + evolocumab 420 Q2W
42 (June 2024)	90-100	Rosuvastatin 40 mg + ezetimibe 10 mg + evolocumab 420 Q2W + bempedoic acid 180 mg
42 (Oct 2024)	30	Rosuvastatin 40 mg + ezetimibe 10 mg + evolocumab 420 Q2W + bempedoic acid 180 mg + evinacumab Q4W
42 (Jan 2025)	36	Rosuvastatin 40 mg + ezetimibe 10 mg + evinacumab Q4W

Abbreviations: LA, lipid apheresis; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; Q4W, every 4 weeks.
[a]LDL-C at nadir.

at age 44, following angina symptoms, coronary angiography demonstrated 3-vessel disease, and he underwent coronary artery bypass graft. From 2009 to 2011, he was switched to the maximally tolerated dose of rosuvastatin (ie, 30 mg), ezetimibe 10 mg, and fenofibrate 145 mg, which initially achieved good lipid control but gradually lost efficacy (mean LDL-C 194 mg/dL). During this period, his body mass index (BMI) increased from 21.8 to 29.1 kg/m^2. Between 2010 and 2011, he was enrolled in a clinical trial with lomitapide (5-20 mg/d), achieving excellent results (LDL-C 44 mg/dL). However, treatment was discontinued due to poor gastrointestinal tolerability (likely related to suboptimal dietary adherence) and progressive hepatic steatosis with elevated transaminases.

Once PCSK9 inhibitors became available, between 2016 and 2018, he received evolocumab (140 mg initially, later 420 mg) administered subcutaneously every 2 weeks, but the response was poor, and therapy was discontinued. Lomitapide was later reintroduced at a lower dose after intensive dietary counseling; however, despite initial lipid improvement, gastrointestinal intolerance persisted, resulting in poor adherence and loss of efficacy. In 2022, obstructive sleep apnea was diagnosed and treated with continuous positive airway pressure. In 2023, echocardiography showed normal left ventricular function (59%), aortic valve stenosis with mild regurgitation, and mild tricuspid regurgitation. BMI had further increased to 34 kg/m². In January 2024, he underwent right carotid endarterectomy.

In April 2024, intravenous evinacumab (15 mg/kg) was introduced every 4 weeks in addition to ongoing statin/ezetimibe/fenofibrate therapy. At baseline, this patient showed extremely elevated TC 636 mg/dL, with LDL-C 549 mg/dL and apoB 305 mg/dL, reflecting a high circulating burden of atherogenic lipoproteins. TG levels were 276 mg/dL, while lipoprotein(a) [Lp(a)] concentration was also above normal (38 mg/dL), further contributing to his cardiovascular risk profile. After 15 months, his time-averaged post-apheresis LDL-C was reduced by 82% by evinacumab compared with baseline (mean LDL-C 62 mg/dL) (Fig 2A and Table). The lowest LDL-C level achieved during evinacumab therapy was 26 mg/dL post-apheresis and 70 mg/dL pre-apheresis. TG levels remained consistently below 150 mg/dL throughout the observation period (time-averaged mean reduction of 85.6%), showing limited variability and greater stability compared with LDL-C, despite occasional deviations from the apheresis schedule. In addition, time-averaged mean reductions included 51.5% in apoB, 32.5% in Lp(a), and 44.8% in HDL-C. No adverse events were reported, except for a mild headache after the first administration of evinacumab.



	apr-24	apr-24	may-24	jun-24	jul-24	aug-24	sep-24	oct-24	nov-24	dec-24	jan-25	feb-25	mar-25	apr-25	may-25	jun-25	jul-25	aug-25	sep-25
preLA	549	250	129	110	122	322	118	127	130	119	193	70	173	182	115	90	156	327	289
postLA	233	81	45	35	41	103	35	40	42	38	64	26	58	62	40	41	60	108	103

	oct-24	nov-24	dic-24	jan-25	feb-25	mar-25	apr-25	may-25	jun-25	jul-25	sep-25
LDL-C	103	20	21	30	18	22	42	34	36	37	32

Figure 2. LDL-C levels during evinacumab treatment. (A) Patient 1 and (B) Patient 2. The dashed line indicates the target level of 55 mg/dL, as recommended by the 2019 ESC/EAS Guidelines. Abbreviations: EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LA, lipid apheresis; LDL-C, low-density lipoprotein cholesterol.

Second case

A 43-year-old man of Sardinian origin with ARH was found to be homozygous for the *LDLRAP1* gene variant (NM_015627.3): c.431dup (p.His144Glnfs*27), that is, the same variant identified in the first case. Molecular analysis was performed already at age 16, but in 2025, it was repeated using NGS, which confirmed the diagnosis and identified an additional rare heterozygous variant in *LDLRAP1*, c.65G > A (p.Trp44*). This latter variant results in the substitution of a tryptophan residue at position 44 with a premature stop codon, leading to a truncated protein. This variant is classified as pathogenic in the ClinVar database. The patient was also a carrier of the APOE ε2/ε2 genotype.

HoFH was clinically diagnosed at age 9, when TC > 700 mg/dL and eruptive tendon xanthomas were observed by a pediatrician. These subsequently regressed following the initiation of LA at age 10. Coronary angiography performed at that time revealed no significant atherosclerotic plaques. From 1997 to 2006, the patient was treated with atorvastatin, starting at 20 mg and later increasing to 60 mg daily, with excellent compliance but inadequate reduction in LDL-C levels (remaining > 250 mg/dL). During this period, he did not undergo regular LA, receiving treatment only once a month or every 2 months. In

2007, at the age of 25, therapy was switched to simvastatin 40 mg plus ezetimibe 10 mg, along with regular LA every 2 weeks, achieving good post-LA LDL-C levels (< 100 mg/dL).

The patient was referred to our Lipid Clinic at age 29. From 2012 to 2016, he reported increasing difficulty in maintaining regular LA sessions due to issues related to quality of life and work commitments. At age 35, when PCSK9 inhibitors became available, his therapy was switched to rosuvastatin 40 mg, ezetimibe 10 mg, and evolocumab 420 mg administered subcutaneously every 2 weeks. This regimen produced highly satisfactory results, with pre-apheresis LDL-C levels ranging from 90 to 100 mg/dL. Consequently, LA was discontinued. In December 2023, at age 41, a coronary computed tomography scan (calcium score 363) revealed extensive and marked atheromatosis in the proximal and mid segments of the anterior interventricular artery, with poor opacification from the ostium to the second septal branch over a 24-mm segment. These findings were consistent with a probable chronic total occlusion due to calcific atheromatosis, with evidence of collateral circulation between the anterior interventricular and posterolateral branches. The common trunk was free of significant stenosis. Subsequently, in June 2024, myocardial scintigraphy revealed no perfusion defects either at rest or after stress. Lipid-lowering therapy (LLT) was therefore intensified with the addition of bempedoic acid. In October 2024, monthly infusions of evinacumab (15 mg/kg) were initiated. At baseline, the patient exhibited a much milder lipid profile compared with the previous case, with TC 160 mg/dL and LDL-C 103 mg/dL. TG levels were low (42 mg/dL), while apoB was 107 mg/dL. Lp(a) concentration was 14 mg/dL. After 3 months of therapy, evolocumab 420 mg every 2 weeks and bempedoic acid 180 mg daily were discontinued due to a reduction in TC to 55 mg/dL. The patient has continued treatment with evinacumab in combination with rosuvastatin 40 mg and ezetimibe 10 mg. After 10 months, LDL-C levels have remained below 55 mg/dL (Fig 2B and Table), with a time-averaged LDL-C decrease of 73.8%. In addition, time-averaged mean reductions included 32.8% in TGs, 52.8% in apoB, 57.1% in Lp(a), and 36.6% in HDL-C. No adverse effects were reported, except for a transient episode of abdominal colic following the first infusion, which resolved spontaneously without the need for any therapeutic intervention.

Discussion

The most effective treatment for patients with ARH has seldom been the object of detailed evaluation. ARH is a rare form of HoFH, with predominance in the Mediterranean area. Both patients described are of Sardinian origin. Very recently, a series of 71 Spanish patients with FH listed 4 *LDLRAP1* carriers, with different variants (1613 bp-deletion, c.207 delC, c.431dupA[8]), who interestingly displayed some of the highest LDL-C levels in the whole series of patients with HoFH. In these patients, treatment with statins and PCSK9 inhibitors is described, and patients appeared to have a similar lipid response and survival free of ASCVD events as FH.[8]

One of the 2 patients examined in this report underwent an endarterectomy at age 42, followed by a coronary bypass at age 44. The other patient, while undoubtedly carrying a significant burden of coronary damage, did not experience any acute event or surgical procedure.

These 2 cases, both homozygous for the *LDLRAP1* c.431dup (p.His144Glnfs*27) variant, but differing in their overall genetic background due to the presence of an additional heterozygous *LDLRAP1* variant in case #2, clearly demonstrate how timing and intensity of lipid-lowering therapy can critically determine long-term outcomes in ARH. The first patient, born decades earlier, experienced an inevitably delayed introduction of modern LLT. This delay was complicated by poor adherence, limited tolerance to effective therapy (lomitapide), and a progressive increase in body weight. Over time, he developed metabolic and inflammatory comorbidities, along with markedly elevated apoB and Lp(a) levels, all contributing to a substantially higher atherogenic burden. These factors likely explain the early onset of clinically manifest ASCVD and the need for revascularization procedures in his forties. By contrast, the second patient benefited from a much earlier exposure to lipid-lowering interventions, including regular apheresis during adolescence and early combination therapy with statins, ezetimibe, and PCSK9 inhibition, maintaining LDL-C levels around 90 to 100 mg/dL well before the introduction of evinacumab. Moreover, the APOE ε2/ε2 genotype may have further modulated his response to LLT.[9,10] The absence of obesity or hepatic steatosis in this patient likely provided additional metabolic protection.

As expected in ARH, the response to PCSK9 inhibitors was variable and generally modest, reflecting limited LDL-R–mediated clearance. In contrast, evinacumab, acting through LDL-R–independent pathways, proved to be highly effective in both cases. In the Evinacumab Lipid Studies in Patients with Homozygous Familial Hypercholesterolemia (ELIPSE) HoFH trial, LDL-C responses to evinacumab showed wide interindividual variability without clear genotype-specific differences.[7] Notably, only 2 patients with ARH were included, and their LDL-C reductions fell within the overall response range of the HoFH population. The LDL-C–lowering effect of evinacumab is mechanistically expected due to its LDL-R–independent mode of action; however, the magnitude of LDL-C reduction observed in our patients exceeded that reported in clinical trials.[11] Although quality of life was not systematically assessed using validated instruments, the marked lipid-lowering efficacy, particularly the achievement of reductions previously unattainable, was associated with a subjective improvement in the patients' perception of their disease.

The significance of the reported cases is the described feasibility of an evinacumab-based pharmacological treatment for patients with ARH, also without LA.

These cases underscore the significance of expeditious identification of patients with HoFH and the initiation of intensive LLT at the earliest stage, with a view to mitigating disease progression. Basic treatments for ARH remain statins, ezetimibe, and PCSK9 antagonists, with the addition of either lomitapide or bempedoic acid. The addition of evinacumab provided unexpected benefit, with LDL-C normalization and apparent potential for a lifelong follow-up. Monitoring of maintenance of the present therapy will provide more definitive data on the efficacy of this pharmacological treatment for ARH.

Implications for clinical practice

Evinacumab appears to be a safe and very effective drug for the treatment of the very rare severe hypercholesterolemia consequent to biallelic *LDLRAP*1 pathogenic variants. It may be safely added to standard lipid-lowering therapy and has the potential to reduce or even eliminate the need for LDL apheresis in some patients.

CRediT authorship contribution statement

Giuliana Germana Mombelli: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Chiara Pavanello:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Francesco Vicari:** Writing – review & editing. **Chiara Moschetti:** Writing – review & editing. **Antonia Alberti:** Writing – review & editing, Supervision. **Laura Calabresi:** Writing – review & editing, Funding acquisition. **Cesare Riccardo Sirtori:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition.

Ethical approval

The work was carried out with the patients' approval and their written informed consent.

Declaration of generative AI and AI-assisted technologies in the writing process

Artificial intelligence tools (specifically, OpenAI) were used to improve the English language of this manuscript. The authors reviewed and approved all AI-assisted edits to ensure accuracy and appropriateness.

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Declaration of competing interest

CP received lecture honoraria from Ultragenyx. The other authors declare no conflicts of interest. No financial support was received for this study.

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