ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–8
https://doi.org/10.1093/ehjcr/ytad029

CASE REPORT
Coronary intervention

Atherosclerotic plaque regression in homozygous familial hypercholesterolaemia: a case report of a long-term lipid-lowering therapy involving LDL-receptor-independent mechanisms

Etienne Khoury [1], Alex Lauzière[1,2], Frederick J. Raal[3], John Mancini[4], and Daniel Gaudet [1,2]*

[1]Lipidology Unit, Community Genomic Medicine Center, Department of Medicine, Université de Montréal and ECOGENE-21 Clinical and Translational Research Center, 930 Jacques-Cartier Est, Chicoutimi, Québec, Canada G7H 7K9; [2]Lipid Clinic, Chicoutimi Hospital, Chicoutimi, Québec, Canada; [3]Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; and [4]Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Received 10 May 2022; first decision 23 June 2022; accepted 11 January 2023; online publish-ahead-of-print 17 January 2023

Background Homozygous familial hypercholesterolaemia (HoFH) is a rare and life-threatening genetic disease characterized by extremely elevated low-density lipoprotein cholesterol (LDL-C) levels, important xanthomatosis and increased risk of premature atherosclerotic cardiovascular disease. Management of HoFH at an early stage is recommended but conventional lipid-lowering therapies (LLTs) dependent on the LDL-receptor for clearance of LDL particles, are usually not sufficient. However, agents acting independently of the LDL-receptor, such as inhibitors of microsomal triglyceride transfer protein (MTP) or angiopoietin-like protein 3 (ANGPTL3), administered in combination, on top of standard-of-care LLT constitute a promising therapy for HoFH.

Case summary The present case describes a long-term (>10 years) follow-up of a 52-year-old woman with severe HoFH, who was treated with conventional lipid-lowering medications (i.e. statins and ezetimibe) for several years before experiencing the risks and benefits that were encountered with the use of LDL-receptor-independent agents (MTP and ANGPTL3 inhibitors). This combination therapy demonstrated a good long-term safety and efficacy profile, while continuous monitoring of hepatic enzymes (sometimes requiring dose adjustments) and fat accumulation is recommended when using lomitapide.

Discussion Treating this HoFH patient with an LLT involving the combination of MTP and ANGPTL3 LDL-receptor-independent inhibitors (lomitapide and evinacumab, respectively) showed remarkable improvement in LDL-C levels, disappearance of xanthomatosis and regression in atherosclerotic plaques. In addition to safety and efficacy, one should question the affordability and access hurdle that emerging combination of expensive therapies might constitute in the future for the payers. These challenges could eventually limit the clinical use of those innovative treatments despite their clinical benefit.

Keywords Homozygous familial hypercholesterolaemia • Microsomal triglyceride transfer protein inhibitor • Angiopoietin-like protein 3 inhibitor • Lomitapide • Evinacumab • Atherosclerosis • Drug safety and efficacy • Plaque regression • Case report

ESC Curriculum 3.1 Coronary artery disease • 8.3 Dyslipidaemia • 8.6 Secondary prevention

* Corresponding author. Tel: +1 418545 1252, Fax: +1 418 545 1604, Email: daniel.gaudet@umontreal.ca
Handling Editor: David Oxborough
Peer-reviewers: Georgios A Christou; Roman Komorovsky
Compliance Editor: Pok-Tin Tang
Supplementary Material Editor: Michael Waight

Learning points

- Early diagnosis and initiation of pharmacotherapy in HoFH is recommended; however, patients rarely achieve the LDL-C target level when treated with conventional LDL-receptor-dependent lipid-lowering agents.
- A therapy including LDL-receptor-independent agents (MTP inhibitor and ANGPTL3 inhibitor) on top of conventional therapies may constitute a promising combination therapy for patients with HoFH.
- Precision medicine is successfully delivering first-in-class agents to the clinical settings; however, access to these agents remains challenging and effective options to provide accessible and affordable treatments to patients with such life-threatening condition should be highly considered.

Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare inherited disease mainly caused by loss-of-function mutations in both copies of the low-density lipoprotein receptor (LDL receptor) gene.[1] This severe form of FH is characterized by lack of LDL-receptor bioavailability, excessively elevated levels of LDL cholesterol (LDL-C) and increased risk of premature coronary artery disease (CAD).[2] On one hand, if left untreated, HoFH patients would reach >500 mg/dL (12.9 mmol/L) of LDL-C plasmatic concentrations during young age, leading to early onset atherosclerosis occurring during childhood and leaving slight chances of survival past 30 years.[3] On the other hand, treating HoFH patients with conventional LDL-receptor-dependent lipid-lowering therapies (LLTs), including statins and ezetimibe, often show attenuated responses to such treatments, and rarely meet the recommended target of LDL-C levels. Therefore, many efforts are still required in order to assess unmet medical needs in HoFH by delivering LDL-receptor-independent strategies.

Lomitapide is a small molecule that inhibits microsomal triglyceride transfer protein (MTP) function and is currently approved in the European Union, the USA, Canada, Mexico, and Taiwan for the treatment of HoFH as an adjunct to other lipid-lowering agents and low-fat diet.[4] This inhibitor specifically blocks the assembly of apoB-containing lipoproteins in the liver and the intestine, which leads to a decrease in the hepatic synthesis of very low-density lipoproteins, thus diminishing LDL-C concentrations.[5–7] Another interesting target, which is mainly involved in the increase of triglycerides and other lipids levels, is the angiopoietin-like 3 (ANGPTL3), known to inhibit lipoprotein lipase and endothelial lipase.[8,9] A fully monoclonal antibody against ANGPTL3, evinacumab, underwent advanced clinical development and was shown to be safe and effective in combination with standard-of-care LLTs in HoFH under a Phase 2 proof-of-concept trial[10] and the Phase 3 ELIPSE study.[11] Evinacumab was approved by the Food and Drug Administration on 11 February 2021 as the first-in-class therapy for the treatment of patients with HoFH as an add-on to LLT. Both MTP-inhibition and ANGPTL3-inhibition mechanisms of action in HoFH are LDL-receptor independent.

Here, we report a case of an HoFH female patient, one of the first to be treated with both agents (>10-year follow-up), showing lipid-lowering responses over long-term treatment of quadruple therapy including two LDL-receptor-independent agents [MTP and ANGPTL3 inhibitors; dual therapy (statin + ezetimibe): 9 years; triple therapy (+lomitapide): 6 years; quadruple therapy (+evinacumab): 5 years]. Overall, this paper addresses long-term efficacy (i.e. lipid-lowering effects and carotid plaque assessment) and highlights safety and tolerability features encountered in 'real-life' settings or under clinical trial development by using a combination of two LDL-receptor-independent therapies in HoFH.

Timeline

Date	Cardiovascular assessments/reported events and lipid-lowering treatment regimen
June 1982	Patient diagnosed at the age of 14 with HoFH based on clinical criteria (LDL-C values, family history of premature CAD, and extensive xanthomatosis).
1990s	With the development of molecular testing, it was confirmed that the patient was homozygous for the c.259T>G (Trp87Gly) binding defective mutation in the LDL-receptor gene.
April 1994	Echography and carotid ultrasound showing atheromatous plaque located at the brachiocephalic vessel (left side dominant); stenosis (80% left and 50% right) of the internal carotid artery.
July 2000	Patient treated with a high-intensity statin (atorvastatin 80 mg) and ezetimibe (10 mg).
January 2005	Abdominal computed tomography (CT) scan showing aortic atheromatosis at early stage without aneurysmal dilatation signs.
March 2005	Coronary angiography showing coronary heart disease with signs of diastolic dysfunction; severe stenosis at the ostium of the right coronary artery.
April 2005	Angioplasty; dilation of the right coronary artery using taxus.
February 2008	Echocardiography showing mild aortic disease with normal left ventricular function and no sign of hypertrophy.
November 2009	Start of lomitapide treatment (initial dosing of 5 mg and gradually increasing to 20 mg).
October 2010	Echocardiography showing mild aortic valve stenosis; aortic and mitral valve regurgitation (2/4); normal left ventricular systolic function.
January 2011	Carotid angiography showing unusual atheromatosis at early stage resulting in distal stenosis (60–65%) of the left common carotid artery; proximal stenosis (39% left and 20% right) of the left internal carotid artery; moderate stenosis of the right external carotid artery.
April 2012	Abdominal CT scan showing calcification of the coronary arteries and thoracoabdominal aorta at early stage; mild calcification at the visceral branches of the abdominal aorta.
October 2012	Abdominal CT scan showing concentric atheromatosis

Continued

Continued

Date	Cardiovascular assessments/reported events and lipid-lowering treatment regimen
	with extensive calcification and several visceral branches in abdominal aorta without aneurysmal dilatation signs.
December 2012	Echocardiography showing moderate stenosis; non-dilated left ventricle; extensive mitral annular calcification; aortic valve calcification; mild tricuspid regurgitation; mild pulmonic regurgitation (2/4).
January 2013	Coronary artery bypass grafting (CABG) and modified Bentall procedure: quadruple bypass: left coronary artery, resection of the aortic arch, left carotid artery, and left axillary artery.
February 2013	Dose adjustment of lomitapide due to gastrointestinal-related side effects [nausea (moderate) and diarrhoea (moderate)].
September 2013	Abdominal CT scan showing concentric atheromatosis with extensive calcification in the abdominal aorta.
March 2014	Dose adjustment of lomitapide due to aspartate transaminase (AST; 80 U/L) and alanine transaminase (ALT; 70 U/L) increased levels.
November 2015	Start of evinacumab treatment [250–450 mg subcutaneous (SC) and 15 mg/kg intravenous (IV) injections].
November 2019	Dose adjustment of lomitapide due to increased international normalized ratio (INR).

Case presentation

The patient is a 52-year-old French-Canadian female with an FH-causing variant in both alleles of the *LDL-receptor* gene [c.259T>G (Trp87Gly)], coding for a loss-of-function mutation in the LDL-receptor. From a father who died at the age of 52 due to cardiovascular disease and a grandfather known to have CAD, one would easily assume that the patient had high risk of CAD that could occur during early age. She was diagnosed with HoFH during childhood, presenting severe phenotype features (e.g. angina, coronary heart disease, stenosis of the carotid arteries) (see Timeline) associated with extremely elevated plasmatic levels of LDL-C, such as apparent arcus senilis, obvious xanthelasma in both eyes, and significant tuberous/tendinous xanthomas (no concurrent medical conditions are reported; *Figure 1*). Around the age of 14, the patient's total cholesterol and LDL-C levels peaked at 23 mmol/L (889 mg/dL) and 21.3 mmol/L [823 mg/dL; normal reference range of LDL-C (0.0–3.4 mmol/L)], respectively. The patient was diagnosed with CAD during her twenties, suffered from angina pectoris and underwent angioplasty of the right coronary artery in her thirties as well as a CABG at the age of 45.

The patient underwent conventional LLTs (i.e. statins and ezetimibe) for many years [statins (atorvastatin up to 80 mg daily/rosuvastatin up to 40 mg daily) for 13 years; ezetimibe (up to 10 mg daily) for 9 years)]; however, LDL-C concentrations never reached the recommended target levels with a mean of LDL-C at 755 mg/dL (19.53 mmol/L; during pregnancy at age 32; *Figure 2*). In November 2009, the patient was enrolled in a single-arm, open-label, Phase 3 study (NCT00730236) starting with 5 mg of lomitapide treatment and the dose was then escalated to 20 mg during the following year.[12] Lomitapide reduced LDL-C levels by 68.3% [from 658 to 205 mg/dL; i.e. 16.76–5.31 mmol/L; *Figure 2A and B*] and non-high-density lipoprotein cholesterol (non-HDL-C)

Figure 1 The effect of long-term microsomal triglyceride transfer protein inhibitor and angiopoietin-like protein 3 inhibitor combination therapy on xanthelasma. Shown are the patient's xanthelasma at baseline (statins + ezetimibe), 6 years post-lomitapide treatment (2015) and 5 years post evinacumab (2020).

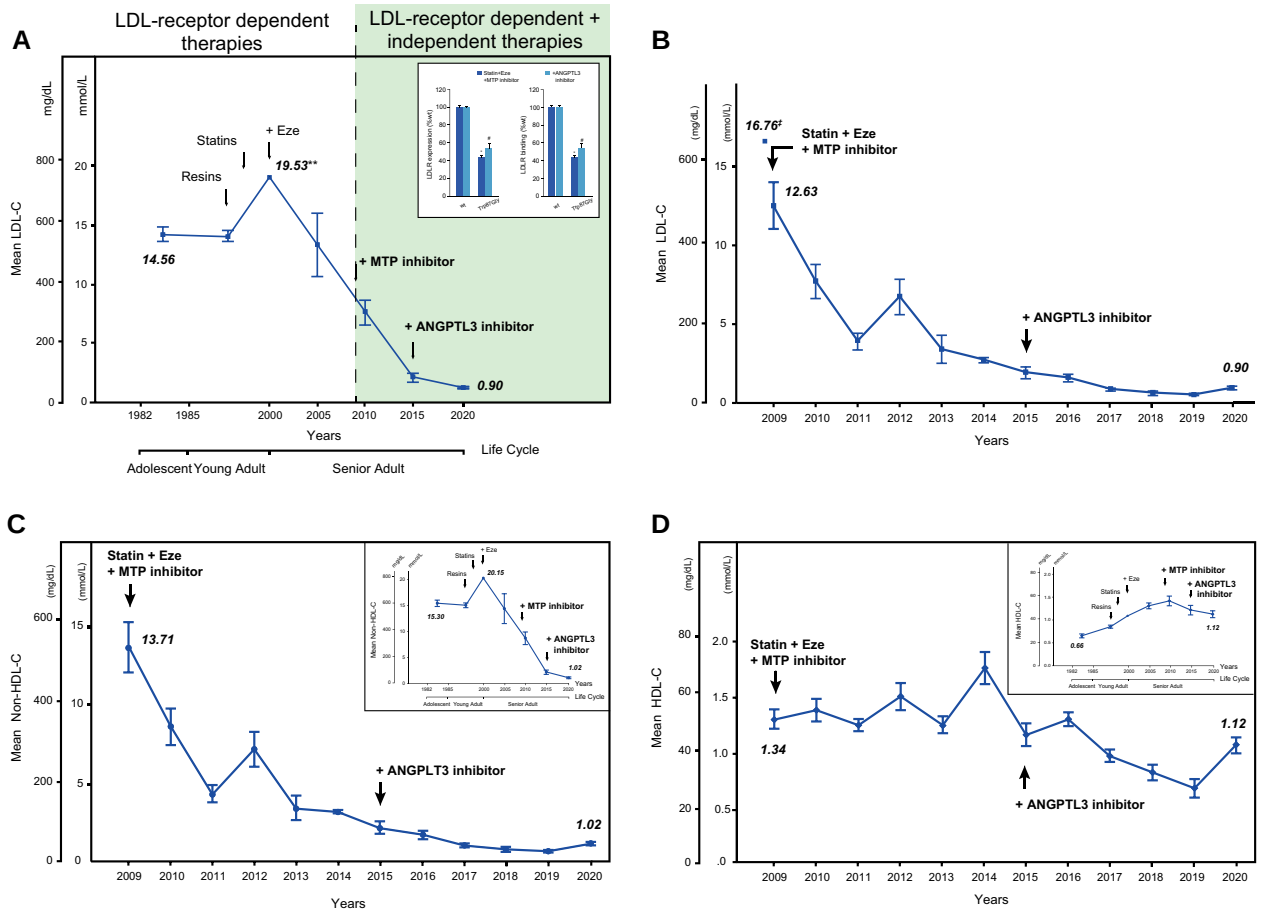


Figure 2 Long-term lipid-lowering efficacy of the combination therapy (microsomal triglyceride transfer protein and angiopoietin-like protein 3 inhibitors) as an add-on treatment in homozygous familial hypercholesterolaemia. (*A*) Shown are the mean low-density lipoprotein cholesterol levels since the patient's first visit at the clinic (treatment naive; 1982) until 2020 (on quadruple therapy: statin + ezetimibe + microsomal triglyceride transfer protein inhibitor + angiopoietin-like protein 3 inhibitor). An illustration of the low-density lipoprotein-receptor expression and binding percentage of the patient's familial hypercholesterolaemia–causing mutation (Trp87Gly) using wild-type low-density lipoprotein receptor as a positive control and comparing % before and after the evinacumab treatment is also presented (top inset). The green zone shows the initiation of lipid-lowering therapies based on low-density lipoprotein-receptor-independent pathways. (*B–D*) According to each selected year, the mean levels of low-density lipoprotein cholesterol (*B*), non-high-density lipoprotein cholesterol (*C*), and high-density lipoprotein cholesterol (*D*) are shown across lomitapide and evinacumab treatments. A lifespan presentation of non-high-density lipoprotein cholesterol and high-density lipoprotein cholesterol is also shown across different lipid-lowering agents, including resins, statins, and ezetimibe (top insets). *When compared with wild-type low-density lipoprotein receptor with statin + ezetemibe + microsomal triglyceride transfer protein inhibitor treatments. #When compared with wild-type low-density lipoprotein receptor with statin + ezetimibe + microsomal triglyceride transfer protein inhibitor + angiopoietin-like protein 3 inhibitor treatments. Statistical significance is defined with a *P*-value <0.05. **Statin and ezetimibe were temporarily stopped during pregnancy. ‡Low-density lipoprotein cholesterol level from 2009 as a pre-treatment baseline.

levels by 67.4% [from 670 to 218 mg/dL; i.e. 17.33–5.65 mmol/L; *Figure 2C*] but did not show significant changes in HDL-C levels (*Figure 2D*) when compared with baseline. Afterwards, the patient was admitted through the prolongation programme (Phase 3 extension trial) and continued her treatment (20 mg/day) after lomitapide was approved on the market. Moreover, in 2015, evinacumab was added to the triple therapy (statin, ezetimibe, and lomitapide) via Phase 2 clinical trial (NCT02265952), and the patient was then treated (IV infusion at 15 mg/kg of body weight) under Phase 3 clinical study (NCT03399786). The combination of lomitapide and evinacumab has revealed remarkable improvement of the patient's lipid profile showing >90% decrease of LDL-C levels [mean levels = 34.80 mg/dL (0.90 mmol/L) in 2020] reaching a minimum concentration of 10.83 mg/dL (0.28 mmol/L).

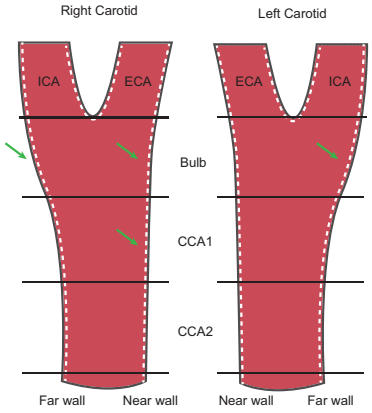
The combination therapy of an MTP and ANGPTL3 inhibitors also showed a clear regression of tendinous xanthomas and xanthelasma in both eyes, as a consequence of diminished levels of cholesterol (*Figure 1*). Another important finding showing evidence of lipid mobilization is the evaluation of plaque deposition in carotid arteries. The comparison of carotid plaques between 2-year (2011), 4-year (2013) post-lomitapide and combination therapy (lomitapide + evinacumab) (2020) showed a net regression of 35.6% on the basis of 4 serially images segments, and cessation of progression in other lesions, as presented in *Figure 3*.

In terms of safety features, the MTP inhibitor exhibited several mild-to-moderate adverse effects commonly related to the gastrointestinal tract, as well as INR increase. Several episodes of diarrhoea and nausea were reported from the patient over the course of lomitapide

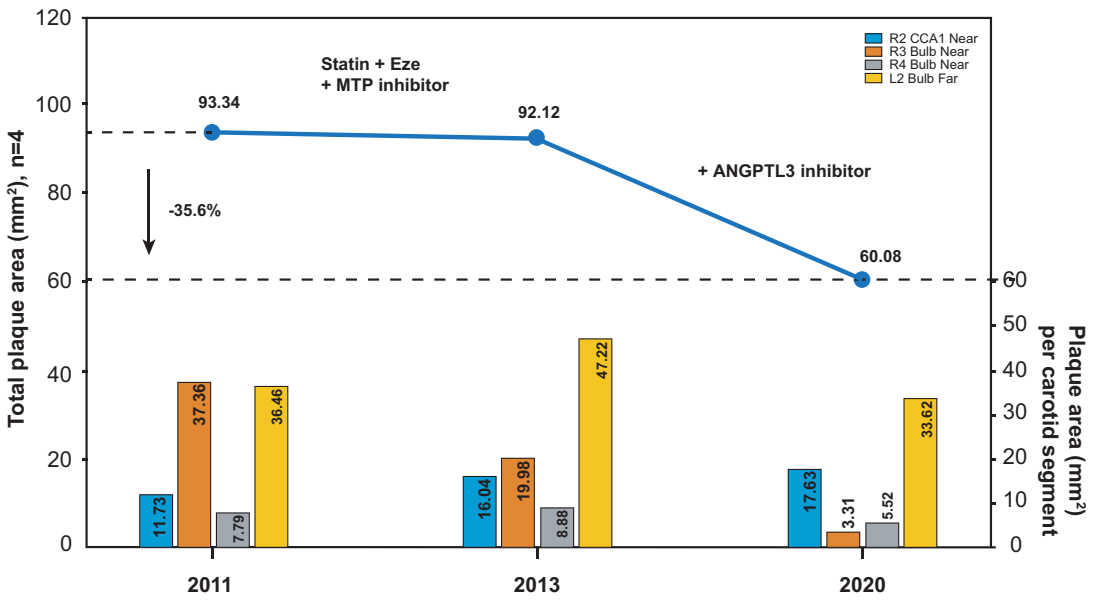
A

Plaque area (mm^2)	2011	2013	2020
Right carotid			
CCA2 NEAR	12.28	-	17.93
CCA1 NEAR	11.73	16.04	17.63
BULB NEAR	37.36	19.98	3.31
BULB FAR	7.79	8.88	5.52
ICA FAR	-	-	26.02
Left carotid			
BULB NEAR	6.21	21.87	10.91
BULB FAR	36.46	47.22	33.62
ICA NEAR	29.31	-	36.86
ICA FAR	5.92	6.48	-
CCA2 FAR	-	-	8.40

B



C



D

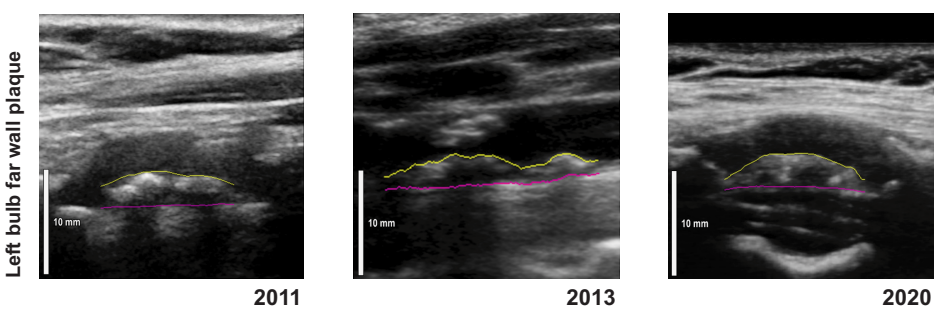
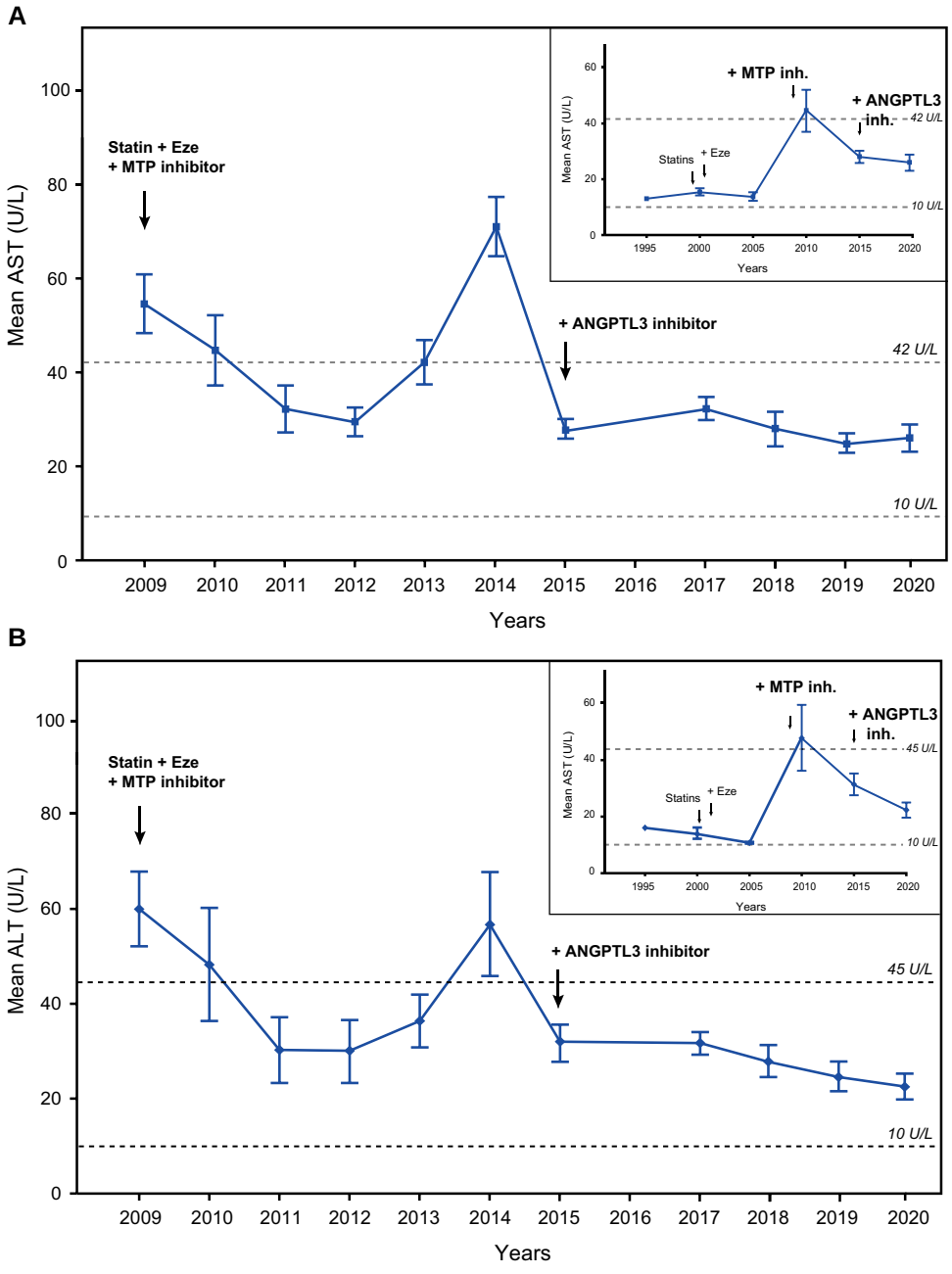


Figure 3 The effect of long-term treatment of microsomal triglyceride transfer protein inhibitor and angiopoietin-like protein 3 inhibitor combination therapy on atheromatous plaque regression. (*A*) Table presenting plaque areas at the right and left carotid segments. Four segments (Right carotid: CCA1 near, bulb near, bulb far; Left carotid: bulb far) were selected for quantifying plaque regression across time. Missing measurements were shown as empty cases, due to low quality of selected images. (*B*) Illustration of four selected carotid regions from which serially imaged plaques were measured across time. (*C*) Shown are total plaque areas (mm^2) of four selected segments (left *y*-axis, top insets) as well as per carotid segment (right *y*-axes, bottom insets), showing frank regression (35.6%) of plaque when comparing 2020 to 2011. (*D*) Representative images showing the regression of the atheromatous plaque at the left bulb segment from the far wall of the carotid. These carotid ultrasound images were captured at the age of 43 [in 2011 (2 years post-lomitapide)], 45 [in 2013 (4 years post-lomitapide)], and 52 [(in 2020 (5 years post-evinacumab)].



FibroScan results	05/2019	09/2019	07/2020	09/2020
CAP (dB/m) (±SD)	163 ± 16	216 ± 30	289 ± 24	270 ± 39
E (kPa) (±SD)	4.2 ± 0.3	3.6 ± 0.4	4.0 ± 0.4	3.5 ± 0.3

Figure 4 Long-term safety evaluation of the combination therapy (microsomal triglyceride transfer protein and angiopoietin-like protein 3 inhibitors) as an add-on treatment in homozygous familial hypercholesterolaemia. According to each selected year, the mean levels of aspartate transaminase (*A*) and alanine transaminase (*B*) are shown across different treatment regimen, including statins, ezetimibe, microsomal triglyceride transfer protein inhibitor and angiopoietin-like protein 3 inhibitor. (*C*) Shown are results of liver steatosis and fibrosis obtained by a specialized ultrasound-based machine (fibroscan). A lifespan presentation of both aspartate transaminase and alanine transaminase levels is also shown across different lipid-lowering agents, including resins, statins, and ezetimibe (top insets).

treatment, but most side effects were manageable with dose adjustments (dose reduced from 20 to 5 mg; see Timeline) and diet control (low-fat diet in order to reduce fat-soluble vitamins absorption with loimtapide). No additional safety events were reported during the evinacumab treatment process. Regarding the effect on the liver function, lomitapide increased AST (82 and 80 U/L) and ALT (159 and 70 U/L) levels on several occasions (2010 and 2014, respectively), but otherwise hepatic enzyme levels remained under the ULN for most of the treatment period. Whenever transaminase levels reached >1.5× ULN, dose adjustment led to a prompt decrease of the hepatic enzymes levels (*Figure 4*). Previous studies have suggested that transaminase elevations would be due to lomitapide-induced hepatic injuries which could cause steatohepatitis over long-term treatment.[13] Here, we illustrate results of transient elastography performed by fibroscan: a specialized ultrasound-based machine that measures liver steatosis (controlled attenuation parameter dB/m) and fibrosis (kPa). The evaluation demonstrated moderate grade of steatosis (*Figure 4C*) without presence of fibrosis, therefore, supporting the evidence that this quadruple therapy would probably not induce serious liver side effects over long-term treatment for this patient. However, continuous monitoring of hepatic fat accumulation is ongoing.

Discussion

The present case describes a long-term (>10 years) follow-up of a patient with severe HoFH, who was treated with conventional lipid-lowering medications (i.e. statins and ezetimibe) for several years before experiencing the risks and benefits that were encountered with the use of LDL-receptor-independent agents (MTP and ANGPTL3 inhibitors). The protein expression and binding activity of the LDL receptor, illustrating the differences (%) before and after the evinacumab treatment has been recently published[14] and strongly suggest that the observed LDL-C-lowering effect is not dependent on an LDL-receptor-associated pathway (green zone and upper inset of *Figure 2A*).

The report described here presents one of the first cases worldwide to be administered with a combination of MTP and ANGPL3 inhibitors, when agents were still used under clinical trial settings. From an extremely elevated baseline of LDL-C levels [21.3 mmol/L (823 mg/dL)] that barely responded well to statins, ezetimibe, and resins, this combination therapy significantly reduced LDL-C plasmatic concentrations by >90%. The exposure to high LDL-C concentrations is known to predict cardiovascular risk and based on large trials, such as the ODYSSEY and FOURIER studies, it is now well established that LDL-C absolute reduction caused by effective lipid-lowering agents is proportional to the cardiovascular benefit. In line with these evidence, the improvement in the patient's lipid profile was also supported by a cessation of plaque progression in some lesions of the carotid and frank regression in others. More specifically, one should also note that three (right carotid: bulb near and far, left carotid: bulb far) of the four selected lesions include the carotid bifurcation segments, which reflects the atherosclerotic process, compared with the common carotid lesion mainly caused by hypertension. One limitation to be considered is the number of identified serially imaged plaques in the selected segments of the carotid arteries.

As for the tolerability evaluation of both agents, the risk/benefit ratio of using this quadruple therapy, including agents with LDL-receptor-independent mechanism of action, seems favourable to the patient especially when considering the potential effect on vascular outcomes and noting that no serious adverse events were reported across this long-term treatment. Accumulation of liver fat and recurrent increase of liver enzymes was previously shown to be associated with lomitapide[6,15]; however, here we showed that combination of MTP and ANGPTL3 inhibitors was suspected to be safe in our HoFH patient according to liver steatosis and hepatic enzymes, which were monitored for >5 years since the initiation of the patient's quadruple therapy. The patient continued her treatment regimen beyond 2020 and retained her participation in clinical trials in order to guarantee access to these emerging treatments. In fact, even when precision medicine is successfully delivering first-in-class agents to the clinical settings, access to these agents remains challenging and effective options to provide accessible and affordable treatments to patients with such life-threatening condition should be highly considered, especially that combination therapies are proving to be an interesting solution.

This patient suffered from many sequelae of hypercholesterolaemia at young adult age; particularly from a severe phenotype, including apparent tuberous/tendinous xanthomas and xanthelasma as well as corneal arcus, and from multiple cardiovascular interventions due to the advanced stage of CAD, even when many clinical parameters were within normal ranges, such as body mass index at 28.9, waist/hip ratio 0.75, systolic/diastolic blood pressure 100/70, and no consumption of alcohol nor tobacco. Therefore, it is of interest to present such unmet medical need and show how emerging treatments and combination therapies could reveal life-changing impacts on HoFH patients and probably constitute promising alternatives to overcome this extremely severe condition. However, more efforts should be invested in research in order to shed light on the mechanism of action behind these therapeutic pathways, which could eventually lead to other promising agents, or combination therapies with high lipid-lowering efficacy and an adequate safety profile. The synergy in the lipid-lowering efficacy that was demonstrated within this combination therapy is unique in its kind, and would certainly bring novelty and new ways to the management of HoFH.

Conclusion

In conclusion, combination therapy including LDL-receptor-independent agents, such as an MTP inhibitor (lomitapide) and an ANGPTL3 inhibitor (evinacumab) could be considered as a promising combination therapy in patients with HoFH. The combination of lomitapide and evinacumab showed remarkable reduction in LDL-C, net regression in some lesions of carotid arteries, with low-to-moderate manageable adverse events and without clinically significant side effects on liver. Tolerability issues with lomitapide are manageable in a real-life setting by drug dosage titration and by avoiding high doses.

Lead author biography

Etienne Khoury is a clinical research scientist at the Community Genomic Medicine Centre, Department of Medicine, at the Université de Montréal. He completed his post-doctoral degree in Experimental Medicine and developed broad experience in clinical research and focused expertise in lipidology, fat-related diseases, and metabolic disorders as well as associated risks. Currently leading a scientific programme that aims to identify, via omics approaches, clinically and genetically based variants for cardiovascular disease prevention in familial hypercholesterolaemia.

Supplementary material

Supplementary material is available at *European Heart Journal-Case Reports* online.

Acknowledgments: We want to thank the ECOGENE-21 staff members as well as everyone's contribution to the high-quality of care provided to this patient.

Consent: The authors confirm that a written consent for submission and publication of case report's results including the images and associated text have been obtained from the patient in line with COPE guidance and in accordance with the Declaration of Helsinki.

Conflict of interest: D.G. has been involved as a principal investigator or consultant in pivotal trials in FH for Aegerion, Amgen, Cerenis, Cymabay, Gemphire, HDL Therapeutics, Regeneron, and Sanofi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Funding: None declared.

References

1. Bajaj A, Cuchel M. Homozygous familial hypercholesterolemia: what treatments are on the horizon? *Curr Opin Lipidol* 2020;**31**:119–124.
2. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjærg-Hansen A, Watts GF, Averna M, Boileau C, Borén J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the consensus panel on familial hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014;**35**:2146–2157.
3. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest* 2003;**111**:1795–1803.
4. Blom DJ, Fayad ZA, Kastelein JJ, Larrey D, Makris L, Schwamlein C, Bloeden L, Underberg J; LOWER investigators. LOWER, a registry of lomitapide-treated patients with homozygous familial hypercholesterolemia: rationale and design. *J Clin Lipidol* 2016;**10**:273–282.
5. Stefanutti C. Lomitapide-a microsomal triglyceride transfer protein inhibitor for homozygous familial hypercholesterolemia. *Curr Atheroscler Rep* 2020;**22**:38.
6. Khoury E, Brisson D, Roy N, Tremblay G, Gaudet D. Review of the long-term safety of lomitapide: a microsomal triglycerides transfer protein inhibitor for treating homozygous familial hypercholesterolemia. *Expert Opin Drug Saf* 2019;**18**:403–414.
7. Blom DJ, Gaudet D, Hegele RA, Patel DS, Cegla J, Kolovou G, Marin LM. A case series assessing the effects of lomitapide on carotid intima-media thickness in adult patients with homozygous familial hypercholesterolaemia in a real-world setting. *Adv Ther* 2022;**39**:1857–1870.
8. Fujimoto K, Koishi R, Shimizugawa T, Ando Y. Angptl3-null mice show low plasma lipid concentrations by enhanced lipoprotein lipase activity. *Exp Anim* 2006;**55**:27–34.
9. Rosenson RS, Burgess LJ, Ebenbichler CF, Baum SJ, Stroes ESG, Ali S, Ali S, Khilla N, Hamlin R, Pordy R, Dong Y, Son V, Gaudet D. Evinacumab in patients with refractory hypercholesterolemia. *N Engl J Med* 2020;**383**:2307–2319.
10. Gaudet D, Gipe DA, Pordy R, Ahmad Z, Cuchel M, Shah PK, Chyu KY, Sasiela WJ, Chan KC, Brisson D, Khoury E, Banerjee P, Gusarova V, Gromada J, Stahl N, Yancopoulos GD, Hovingh GK. ANGPTL3 inhibition in homozygous familial hypercholesterolemia. *N Engl J Med* 2017;**377**:296–297.
11. Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, Ali S, Banerjee P, Chan KC, Gipe DA, Khilla N, Pordy R, Weinreich DM, Yancopoulos GD, Zhang Y, Gaudet D; ELIPSE HoFH Investigators. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med* 2020;**383**:711–720.
12. Cuchel M, Meagher EA, du Toit Theron H, Blom DJ, Marais AD, Hegele RA, Averna MR, Sirtori CR, Shah PK, Gaudet D, Stefanutti C, Vigna GB, Du Plessis AM, Propert KJ, Sasiela WJ, Bloedon LT, Rader DJ; Phase 3 HoFH Lomitapide Study investigators. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet* 2013;**381**:40–46.
13. Clinical review(s) of Lomitapide for treating patients with homozygous familial hypercholesterolemia. *FDA Drug approvals and databases*. Washington, DC: FDA/Center for Drug Evaluation and Research; 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203858Orig1s000OtherR.pdf (Last accessed January 2023).
14. Ahmad Z, Banerjee P, Hamon S, Chan KC, Bouzelmat A, Sasiela WJ, Pordy R, Mellis S, Dansky H, Gipe DA, Dunbar RL. Inhibition of angiopoietin-like protein 3 with a monoclonal antibody reduces triglycerides in hypertriglyceridemia. *Circulation* 2019;**140**:470–486.
15. Aljenedil S, Alothman L, Belanger AM, Brown L, Lahijanian Z, Bergeron J, Couture P, Baass A, Ruel I, Brisson D, Khoury E, Gaudet D, Genest J. Lomitapide for treatment of homozygous familial hypercholesterolemia: the Quebec experience. *Atherosclerosis* 2020;**310**:54–63.