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CASE SERIES

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

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ABSTRACT

Introduction: Homozygous familial hypercholesterolaemia (HoFH) is characterised by extremely elevated levels of low-density lipoprotein cholesterol (LDL-C) and results from multiple mutations in genes affecting the LDL receptor pathway. Patients are at risk of premature atherosclerotic cardiovascular disease (ASCVD) and premature death. Lomitapide is a microsomal triglyceride transfer protein inhibitor developed to treat HoFH, but cardiovascular outcome data are lacking.

Methods: We evaluated detailed data from five HoFH patients and one patient with heterozygous FH (HeFH) and a very severe phenotype. We also analysed confirmatory data from a further 8 HoFH cases. In total, we analysed data from patients in seven global centres in six countries who were all treated with lomitapide with long-term follow-up. Carotid intima-media thickness (CIMT) imaging was recorded on an ad hoc basis to monitor ASCVD in HoFH.

Results: Lomitapide resulted in marked decreases in LDL-C of 56.8–93.9% [77.7–93.9% in the 6 initial cases (mean nadir 64.8 ± 30.1 mg/dL); 56.8–86.0% in the 8 confirmatory cases (mean nadir 131.4 ± 38.2 mg/dL)]. CIMT regressed in 50% of cases (mean follow-up 5.0 ± 3.1 years in initial six cases, and 4.4 ± 1.4 years in confirmatory cases). In the remaining patients, CIMT showed little further change. In patients where assessments of plaque area were available, regression or stabilisation in CIMT was accompanied by clinically significant regression of plaque area.

Conclusions: Lomitapide reduces LDL-C levels in patients with HoFH and severe LDL-C phenotypes, and results in stabilisation and/or

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regression of CIMT, which is an established marker of ASCVD risk. Additional data are needed to determine if this confers a survival benefit in these very high-risk patients.

Keywords: Homozygous familial hypercholesterolemia; Lomitapide; Carotid intima-media thickness; Cardiovascular; Low-density lipoprotein cholesterol

Key Summary Points
The principal aim of lipid-lowering therapy in Homozygous familial hypercholesterolaemia (HoFH) is to avert or delay the onset of atherosclerotic cardiovascular disease (ASCVD).
The effect of lomitapide on markers of subclinical atherosclerosis has not been studied in clinical trials
The present case series examines changes in carotid intima-media thickness (CIMT) in 14 patients receiving lomitapide in the normal course of care.
Lomitapide substantially reduced Low-density lipoprotein cholesterol (LDL-C) levels in the patients with HoFH and resulted in stabilisation and/or regression of CIMT
Lomitapide may have the potential to delay or avert ASCVD progression in patients with HoFH

INTRODUCTION

Homozygous familial hypercholesterolaemia (HoFH) is a rare metabolic condition caused by bi-allelic genetic defects in the low-density lipoprotein (LDL) receptor (LDL-R) pathway that lead to impaired uptake of LDL particles by the liver. This results in severely elevated plasma levels of LDL cholesterol (LDL-C) and premature, progressive atherosclerotic cardiovascular disease (ASCVD) [1–3].

The underlying molecular abnormalities resulting in the HoFH phenotype vary between patients. Patients may have homozygous, compound heterozygous or double heterozygous mutations in several genes encoding proteins involved in the LDL-R pathway. At present, HoFH causative mutations have been identified in *LDLR* (encoding LDL-R), *APOB* (encoding apolipoprotein [apo] B), *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9), and *LDLRAP1* (which encodes LDL-R adaptor protein 1). Most patients with HoFH have bi-allelic *LDLR* mutations.

Patients with HoFH usually display extremely elevated levels of LDL-C, but there is marked variability in the severity of the phenotype. Most patients have physical stigmata of hypercholesterolaemia such as tendinous and cutaneous xanthoma and/or corneal arcus [1]. Although ASCVD is generalised in patients with HoFH, the most common clinical manifestations are coronary artery disease and supravalvular as well as valvular aortic stenosis [1]. If HoFH goes untreated, the average age for development of ASCVD is 12.5 years and mean survival is 18 years [4]. To delay or avoid the onset of major, adverse cardiovascular events in HoFH, early diagnosis and effective therapy are critical. The core principle for the treatment of HoFH is to reduce LDL-C levels as much as possible to reduce cumulative LDL-C exposure [1].

The European Atherosclerosis Society has set LDL-C targets for patients with HoFH in line with the notion that ASCVD risk is high or very high in all patients with HoFH. These targets are < 100 mg/dL (< 2.5 mmol/L) in adults and < 135 mg/dL (< 3.5 mmol/L) in children or < 70 mg/dL (< 1.8 mmol/L) in adults with diagnosed clinical ASCVD [1, 4].

Patients with HoFH are generally prescribed high-dose statins and ezetimibe, but statins act mainly by increasing LDL-R expression. As such, this therapeutic approach is much less effective in patients with HoFH compared with patients with other forms of hypercholesterolaemia [1]. Lipoprotein apheresis can further reduce LDL-C, but, due to its intermittent nature, it is often not possible to achieve complete LDL-C control in this manner [1]. The difficulties of adequately

controlling LDL-C in patients with HoFH are well illustrated by data from the TAUSSIG study. TAUSSIG was a large study of well-treated patients with severe heterozygous FH or HoFH [5]. Despite aggressive lipid-lowering therapy (approximately 90% of HoFH patients received high-dose statins, 90% received ezetimibe and 32% were treated with apheresis), baseline LDL-C in HoFH patients was still 329 ± 137 mg/dL. Addition of evolocumab resulted in further reductions in LDL-C at Week 216 of 75 ± 125 mg/dL [5]. These data show that it remains difficult to achieve LDL-C targets in patients with HoFH, even with application of modern pharmacotherapy.

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor, approved as an adjunct to diet and other lipid-lowering agents, with or without apheresis, to reduce LDL-C in adult patients with HoFH [6, 7]. Unlike conventional lipid-lowering agents that exert their LDL-C-lowering effect through upregulation of LDL-R activity, lomitapide acts independently of the receptor by reducing synthesis and subsequent export of apo B-containing lipoproteins from the liver and small intestine [8]. Phase 3 data demonstrated a 50% reduction in LDL-C levels from baseline after 26 weeks of treatment [9]. These results were maintained through the overall planned 78 weeks of the pivotal trial. Currently, lomitapide is not yet available in all countries and access remains difficult for many patients in countries where health care payers do not provide reimbursement for lomitapide.

Despite the correlation of ASCVD risk with cumulative LDL-C exposure, there is very little published information on the effects of lomitapide on stabilisation and/or regression of atherosclerotic plaques and ultimately cardiovascular outcomes. A modelling study of cardiovascular event rates has estimated that the annualised major adverse cardiovascular event (MACE) rate is 2.0% for HoFH patients receiving lomitapide versus 26.1% for matched controls [10]. Carotid intima-media thickness (CIMT) is an established, non-invasive imaging surrogate for detection of subclinical atherosclerosis [11–13]. An image from a typical CIMT echo is given in Fig. 1. We therefore gathered data from clinical cases where CIMT measurements were available in HoFH patients receiving lomitapide with the aim of providing preliminary data on the effects of lomitapide on vascular health.

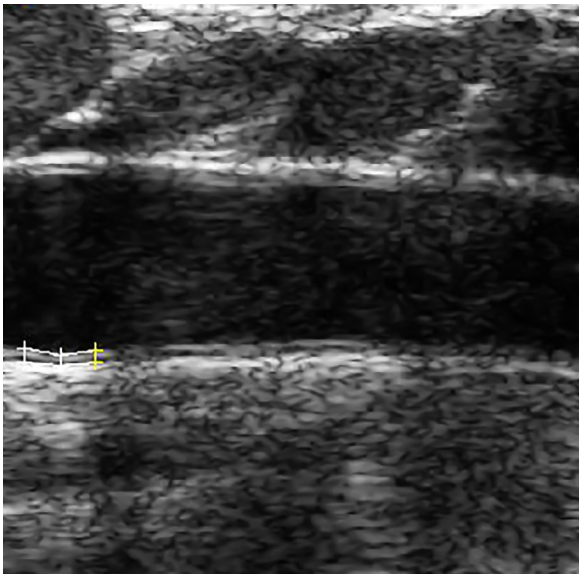

Fig. 1 Image from a typical, normal CIMT ultrasound test of the right common carotid artery. *Central area* shows the arterial lumen; *crosses* (*lower left*) indicate computerised measurement of CIMT. *CIMT* carotid intima-media thickness

CASE PRESENTATION

Seven physicians with extensive experience in the treatment of HoFH provided data from patients treated in the course of normal clinical practice. Patient locations were South Africa, USA, UK, Spain ($n = 1$ for all), Canada ($n = 2$) and Greece ($n = 8$). In almost all cases, and in accordance with the product label, lomitapide was commenced at a low dose (5 mg/day), and gradually escalated. Background lipid-lowering therapy (LLT) was provided according to local practices. In accordance with the lomitapide label, dietary counselling, vitamin E and essential fatty acid supplements were provided. All patients were counselled to observe a diet in which less than 20% of total daily energy was derived from fat. All patients underwent regular

monitoring of liver function, along with other standard laboratory tests.

CIMT was measured according to local practices, and values mostly expressed as a mean of bilateral determinations. Ultrasound equipment and measurement techniques, as well as measurement intervals, differed between patients, which precluded a formal statistical analysis. Therefore, data are presented for individual patients. Baseline LDL-C was recorded at the clinic visit immediately prior to the commencement of lomitapide. LDL-C nadir values were defined as the lowest level achieved after lomitapide was commenced. The Greek patients are presented as a cohort analysis, validating the data from the first six identified cases.

This case series was conducted as a retrospective study of normal patient care and is not subject to Institutional Review Board approval. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All the patients provided written consent for their details to be published in the current case series.

RESULTS

Patient 1

Patient 1 was a man with compound heterozygous p.Asp227Glu (defective) and p.Trp666Ter (null) mutations in *LDLR*. The patient had clinical evidence of atherosclerotic plaques (femoral and aortic vascular bruits) and supravalvular aortic stenosis at age 33 years when he first commenced lomitapide. He had not required surgery for these conditions. At the time lomitapide was commenced, the patient's LDL-C level was 385.5 mg/dL—historical values were not available. The patient was receiving atorvastatin 80 mg/day and ezetimibe 10 mg/day. Lipoprotein apheresis (LA) was conducted every 2 weeks. At this time, carotid ultrasound revealed mean CIMT of 1.18 mm (Supplemental Fig. 1). Lomitapide was commenced at 5 mg/day and escalated over the next 6 months to 40 mg/day. LDL-C levels responded well and were brought down to as low as 80 mg/dL (nadir). Three years after starting lomitapide, LA was stopped, and the patient was maintained on lomitapide 40 mg/day, with the background LLT unchanged. Liver enzymes remained normal throughout. In 2015, 7 years after lomitapide was commenced, a second carotid ultrasound was performed, and modest regression in CIMT to 1.11 mm was noted (Supplemental Fig. 1). LDL-C was maintained at approximately 100–180 mg/dL, with no signs of cardiovascular disease progression. However, approximately 5 years after starting lomitapide, this patient underwent aortic valve and root replacement for supravalvular aortic stenosis. The patient developed fungal infective endocarditis post-surgery, and died following repeat surgery.

Patient 2

Patient 2 is a woman with a homozygous p.Trp87Arg (defective) mutation in the *LDLR*, conferring diminished LDL-R function. At diagnosis (age 14 years), and without LLT, the patient's LDL-C level was 823.7 mg/dL and characteristic xanthomas were evident. The patient had early onset coronary artery disease and had undergone angioplasty with stenting at age 37. At age 41 years, the patient was receiving atorvastatin 80 mg/day, ezetimibe 10 mg/day and aspirin 80 mg/day, but was not receiving LA. LDL-C levels remained high at 580 mg/dL. At this point, lomitapide was commenced at 5 mg/day and escalated to 20 mg/day (Fig. 2). Twelve months later, LDL-C levels had reduced to approximately 200 mg/dL. That month, carotid ultrasonography revealed mean CIMT of 0.82 mm and total plaque area of 147.1 mm^2. Over the next 2 years, LDL-C levels gradually reduced to below 100 mg/dL with a nadir of just 35.2 mg/dL. Carotid ultrasound revealed some regression to CIMT 0.65 mm (Fig. 2) and total plaque area 120.5 mm^2. A coronary artery bypass graft procedure was performed in the same year, and the patient continues to be monitored closely for cardiac progression.

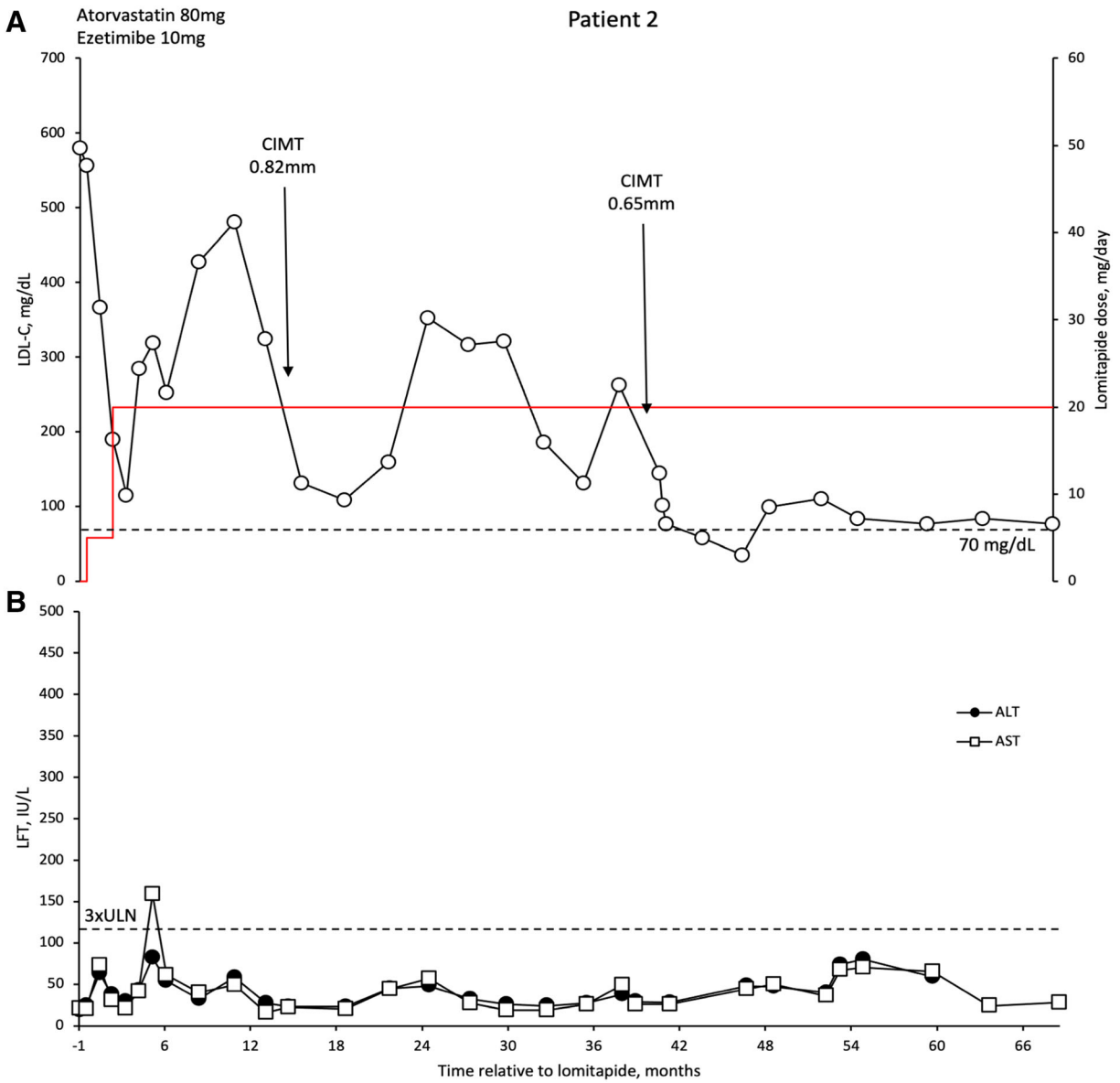

Fig. 2 **A** LDL-C levels, lomitapide dose (*red line*), CIMT, and **B** LFTs in Patient 2. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CIMT* carotid intima-media thickness, *LA* lipoprotein apheresis, *LDL-C* low-density lipoprotein cholesterol, *LFT* liver function test, *ULN* upper limit of normal

Patient 3

Patient 3 is a man with compound heterozygous null mutations; specifically, p.Gln739Ter (null) and an exon 1–6 copy number variation (null deletion). He was diagnosed at age 5 years, when biweekly plasmapheresis was initiated. At the age of 14, his pre-apheresis LDL-C levels were 429.2 mg/dL, and rosuvastatin 40 mg/day, ezetimibe 10 mg/day and aspirin 81 mg/day were added. He entered the open-label phase 3 trial of lomitapide, reaching a final dose of 60 mg/day after titration per study protocol (Supplemental Fig. 2). At that time, carotid ultrasound revealed mean CIMT of 0.76 mm. On the 60-mg dose, LDL-C levels dropped to a

nadir of 95.9 mg/dL and were maintained in the range of 150–430 mg/dL for the next 6 years, with variations related to periods of non-adherence and dietary indiscretion. During this period, there was evidence of regression in CIMT, with values gradually falling to 0.66 mm. Unfortunately, the patient also experienced some elevation of liver function tests (LFTs) to > 3-times the upper limit of normal (ULN), with the greatest peak in AST at 236 IU. Importantly, lomitapide was gradually down titrated to 40 mg/day and then 20 mg/day, and LA was reinstated to once every 2 weeks. LFTs normalised and the LDL-C was maintained in the same range as before. The last carotid ultrasound showed CIMT to be stable at 0.80 mm.

Patient 4

Patient 4 is a man with a heterozygous p.Glu228Ter (null) mutation in *LDLR* and a high polygenic risk score of 16 out of 20, which is in the 99th percentile. LDL-C levels at diagnosis were approximately 350 mg/dL, which is commensurate with a severe heterozygous phenotype. The patient was diagnosed with coronary artery disease and underwent initial coronary artery stenting at age 33 years with a history of cigarette smoking. He presented at age 40 years with unstable angina and underwent stenting of the left circumflex and left anterior descending artery. At this stage, the patient's lipid-lowering therapy was increased from simvastatin 40 mg/day to atorvastatin 80 mg/day.

At a follow-up visit when the patient was 40 years old, his LDL-C was 312 mg/dL. The patient was advised to stop smoking and ezetimibe 10 mg/day was added to existing atorvastatin 40 mg/day. A clinical decision was made to commence off-label lomitapide at 5 mg/day. LDL-C levels rapidly dropped to 128–136 mg/dL (Supplemental Fig. 3). Lomitapide dose was escalated to 30 mg/day, and then adjusted to 20 mg/day. A brief excursion in LFTs > 3-times ULN required a brief down titration to 10 mg/day. Commercial availability then allowed subcutaneous evolocumab 420 mg monthly to be commenced with LDL-C levels persistently above 70 mg/dL. Three years after commencing lomitapide, LDL-C levels reached a nadir of 33 mg/dL. Lomitapide therapy was ceased in January 2017 due to gastrointestinal disturbances, and LDL-C levels immediately increased to ≥ 240 mg/dL. LDL-C levels subsequently reduced again with evolocumab plus background LLT to an LDL-C of 107 mg/dL. Responsiveness to evolocumab would be expected in a patient that has one wild-type *LDLR* allele.

During lomitapide therapy, two assessments of CIMT were made. The first, at age 40 years while the patient was recently commenced on lomitapide 5 mg/day, gave a result of 0.56 mm. The second measure was made 26 months later when the patient was on lomitapide 30 mg/day. This revealed CIMT of 0.57 mm. Total plaque area had, however, regressed from 64.5 to 42.1 mm^2 during the lomitapide treatment period.

Patient 5

Patient 5 is a woman with a homozygous p.Asp227Glu (defective) mutation in *LDLR*. The patient was diagnosed with HoFH at the age of 3 years. At age 39 years, the patient's interval mean LDL-C was 266.8 mg/dL. She was receiving rosuvastatin 40 mg/day, ezetimibe 10 mg/day and colesevelam 375 mg/day. LA was applied weekly and was very awkward for the patient's working life. In the same year, lomitapide was commenced at 5 mg/day and escalated to 10 mg/day 3 months later (Fig. 3). At this point, a mean CIMT reading was found to be 2.7 mm. Lomitapide was escalated to 20 mg/day, and LDL-C levels remained in the range 92–200 mg/dL. LA intervals were gradually extended until lomitapide was escalated to 30 mg/day, enabling cessation of LA with LDL-C levels as low as 46.4 mg/dL (nadir). Carotid ultrasound 9 months later, when the patient was on lomitapide 30 mg/day but still undergoing monthly LA, revealed mean CIMT had

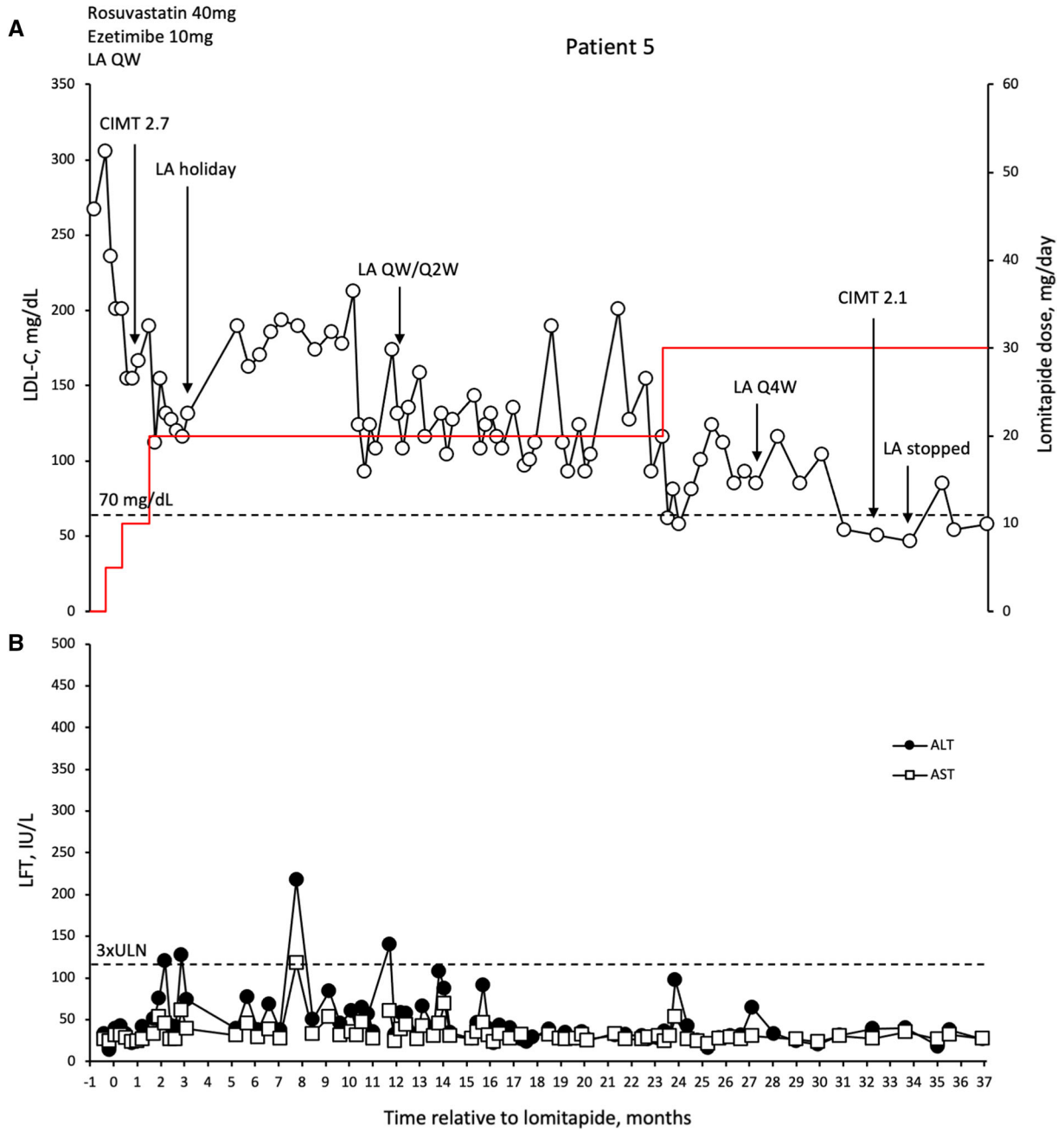

Fig. 3 **A** LDL-C levels, lomitapide dose (*red line*), CIMT, and **B** LFTs in Patient 5. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CIMT* carotid intima-media thickness, *LA* lipoprotein apheresis, *LDL-C* low-density lipoprotein cholesterol, *LFT* liver function test, *QW* once weekly, *Q2W* once every 2 weeks, *Q4W* once every 4 weeks, *ULN* upper limit of normal

regressed to 2.1 mm. LFTs increased temporarily but remained < 3-times ULN and resolved without the need for specific intervention.

Patient 6

Patient 6 is a boy with a homozygous p.Glu228Ter (null/null) mutation in *LDLR*. At

Table 1 Summary of CIMT measurements from baseline to follow-up in all six initial patients

Patient	Baseline CIMT, mm	Last CIMT, mm	Interval between CIMT, years	Interval between lomitapide start and last CIMT, years	Change in CIMT, mm	Net response	Measurement site
1	1.18	1.11	8	7	− 0.08	Regression	RCCA
2	0.82	0.65	2	4	− 0.17	Regression	RCCA, LCCA
3	0.76	0.80	10	9	0.04	Stable	RCCA, LCCA
4	0.56	0.57	2	2	0.01	Stable	RCCA, LCCA
5	2.65	2.05	3	2	− 0.60	Regression	RCCA, LCCA
6	1.81	1.20	5	2	− 0.61	Regression	RCCA, LCCA
Mean	1.30	1.06	4.9		− 0.23		
SD	0.80	0.54	3.3		0.30		
Median	1.00	0.95	3.9		− 0.12		
Min	0.56	0.57	2.0		− 0.61		
Max	2.65	2.05	9.9		0.04		

CIMT carotid intima-media thickness, *LCCA* left common carotid artery, *Max* maximum, *Min* minimum, *RCCA* right common carotid artery, *SD* standard deviation

the age of 8 years, the patient had mean CIMT 1.81 mm against a background of untreated LDL-C levels of 658 mg/dL. The patient was commenced on rosuvastatin 20 mg/day and ezetimibe 10 mg/day. LA was commenced once every 2 weeks later the same year, and CIMT reached 1.39 mm a year later. LDL-C levels decreased to 450 mg/dL over the course of the next 3 years (Supplemental Fig. 4), and some regression of CIMT was evident (i.e. 1.56 mm at 26 months after first CIMT). Forty months after the first CIMT, a repeat CIMT was 1.29 mm and lomitapide was commenced at 5 mg/day and escalated to 40 mg/day in a stepwise fashion. Ten months after starting lomitapide, adjustments were made to the patient's LA schedule such that there was less burden of LA, and he remains on monthly LA. During this period, serial CIMT measures were made, which showed sustained regression of CIMT down to 1.20 mm. LDL-C has been maintained in the range 100–220 mg/dL (nadir 98.0 mg/dL) with no relevant changes in LFTs.

Summary of CIMT data from six core patients

A summary of CIMT measures for all six patients is given in Table 1. There is a general trend towards stabilisation or regression of CIMT in the six core cases (Supplemental Fig. 5).

Differences in ultrasound techniques and analysis protocols between patients means that information on plaque area is not available for most patients. Where these data are available (Patients 2 and 4), modest regression or stabilisation in CIMT was accompanied by clinically significant regression of plaque area (Table 2).

Additional data from Greece

The Greek cohort included five male and three female patients. All patients had markedly elevated LDL-C levels prior to initiation of lomitapide (mean 435.1 ± 94.6 mg/dL; range 345–600 mg/dL), despite use of maximal daily dose of rosuvastatin (40 mg/day plus ezetimibe 10 mg/day). Mean reductions in LDL-C of 69 ± 11% (nadir) were achieved with a mean

dose of lomitapide 31 ± 10 mg/day. Only one patient (Patient 5) experienced elevations in AST and ALT > 3 times ULN. Mean (left and right common carotid arteries) CIMT prior to lomitapide therapy was in the range 0.6–1.1 mm, and CIMT values at follow-up demonstrated general stability of CIMT (change in CIMT 0.04 ± 0.24 mm, with 50% of the patients showing some evidence of CIMT regression (Table 3).

Mutation classifications for all patients are shown in Supplemental Table 1.

Table 2 Summary carotid artery plaque data in two patients

Parameter	Patient	
	2	4
Change in mean CIMT, mm	− 0.17	0.01
Change in total plaque area, mm^2	− 26.6	− 22.39
Change in mean total thickness, mm	0.01	− 0.27
Change in total area, mm^2	− 30	− 22.19
Change in vascular age, years	0	− 10

CIMT carotid intima-media thickness

DISCUSSION

This case series shows that CIMT regresses or stabilises in the majority of HoFH patients treated with lomitapide when LDL-C is controlled. All the patients (including the patient with severe HeFH) in this case series had extremely elevated levels of LDL-C characteristic of HoFH, which were not adequately controlled by conventional lipid-lowering therapy, including LA in many cases.

In all patients, lomitapide resulted in marked decreases in LDL-C levels. At nadir, LDL-C was reduced by 76.5–93.9%. Overall, eight patients (six from the original cohort, and two from Greece) were able to achieve LDL-C levels < 100 mg/dL, and three patients were able to achieve LDL-C < 70 mg/dL.

In the present series, patients were all treated in a real-world setting. Previous experience of case series outside of clinical trials have shown that lomitapide reduces LDL-C levels to the same extent or greater as that seen in phase 3 clinical trials, but with lower doses [14–18]. This likely occurs because the phase 3 trial used a forced titration study design whereby lomitapide doses were escalated until the patient was not able to tolerate the adverse events [9]. In the real world, lomitapide tends to be dosed to reduce LDL-C levels or reduce LA burden, so doses are often lower, titration is slower and the adverse event profile is less severe. In the current series, elevations in LFTs were not uncommon, but all resolved with minimal intervention required.

This case series shows for the first time that the LDL-C lowering brought about by lomitapide also translates into CIMT regression or arrest of progression in patients with HoFH. Until now, the only data indicating that lomitapide might have any effect on long-term cardiovascular and survival outcomes are derived from a modelling analysis that applied lomitapide-associated reductions in LDL-C levels to historical data from a South African cohort in which survival data were available according to LDL-C level. This analysis suggested that additional LDL-C lowering by lomitapide may increase life expectancy in patients with HoFH by 11.2 years and increase time to first MACE by 5.7 years (6.7 years with lifetime exposure to lomitapide) [19].

The case series we have presented has several limitations. There is no control group that did not take lomitapide, and as this is an ultra-rare disease, the sample size is small. One of the patients (Patient 4) did not have HoFH, rather, he had a severe heterozygous FH phenotype, but this does not detract from the value of understanding the CV outcomes for lomitapide in a patient with high LDL-C levels. In addition, we do not have plaque area data in all patients. Nevertheless, the data presented here do enable us to see, for the first time, the effect of lomitapide on vascular health as measured by changes in CIMT.

CIMT is an established surrogate marker for progression of atherosclerotic disease [12, 20–22], and recently was recommended by

Table 3 Summary of LDL-C and CIMT data in eight Greek patients

Patient number	Current age, years	Genotype	Untreated LDL-C, mg/dL	LDL-C before lomitapide, mg/dL	Date Lomitapide commenced	Lowest LDL-C on lomitapide, mg/dL	Baseline CIMT, mm	Last CIMT, mm	Interval between CIMT, years	Change in CIMT, mm	Comments
1	56.0	c.1285G>A	900	600	2015	84	0.65	0.6	5	− 0.05	CABG; AVR; RC endarterectomy; endocarditis
2	31.1	c.1448G>A, c.1646G>A	900	545	2014	135	1.10	1.25	6	0.15	–
3	24.8	c.1285G>A	1100	345	2015	149	0.60	0.85	4	0.25	PCI
4	26.6	c.1285G>A	1050	410	2015	155	0.90	0.6	3	− 0.30	PCI; AVR
5	26.8	c.1285G>A	950	371	2014	74	1.05	0.9	2	− 0.15	AVR; MVR
6	41.9	c.81C>G, c.1646G>A	UNK*	370	2017	120	1.05	1.45	2	0.40	PCI
7	62.8	UNK	750	366	2016	143	UNK	1.1	3	–	Endarterectomy; stenosis; CABG, AVR
8	19.7	c.666C>A, c.1646G>A	1213	474	2016	191	0.60	0.6	4	0.00	AV stenosis
Mean	36.2		980	435		131	0.85	0.92	3.63	0.04	
SD	14.7		153	95		38	0.23	0.32	1.41	0.24	

*Total cholesterol 770mg/dL.

AV aortic valve, *AVR* aortic valve replacement, *CABG* coronary artery bypass graft, *CIMT* carotid intima-media thickness, *F* female, *LDL-C* low-density lipoprotein cholesterol, *M* male, *MVR* mitral valve replacement, *PCI* percutaneous coronary intervention, *RC* right carotid, *UNK* unknown

a 2019 ESC/EAS guidelines committee for assessment of arterial plaque burden [23]. Two large studies—The Rotterdam Study [24] and the Atherosclerosis in Communities (ARIC) Study [25]—are the pivotal studies that established CIMT as a marker for progressive atherosclerotic disease. In the Rotterdam study of 8000 persons > 55 years of age, ultrasound studies produced solid evidence that CIMT measures can be used as an indicator of atherosclerosis [24]. In the ARIC Study of 15,800 adults, high-resolution B-mode ultrasound was able to assess and delineate all stages of atherosclerosis [25]. Subsequent work has built on these findings, and CIMT is now routinely used as an accurate and inexpensive means of assessing cardiovascular progression or regression in pharmaceutical or population cohort studies [12, 20–22].

In the patients described in the current case series, regression of CIMT was seen in 50% of patients, while in the remaining patients, CIMT did not increase further, often over lengthy observation periods. This lack of regression should, however, not be interpreted as a negative finding, and is similar to the lack of regression seen in the ENHANCE study of patients with heterozygous FH treated either with simvastatin 80 mg/day or simvastatin 80 mg/day plus ezetimibe 10 mg/day. In the ENHANCE trial [26], most participants were enrolled from lipid clinics and had been treated aggressively prior to enrolment. Baseline CIMT in ENHANCE was 0.69 mm, much lower than the value of 0.93 mm found in the earlier ASAP trial, which was able to demonstrate regression, and in which most patients had not been exposed previously to aggressive lipid-lowering therapy [27]. These and other trials show that, if the CIMT is not elevated at baseline, it is not possible to demonstrate CIMT regression. However, lack of progression is very encouraging given the natural tendency for atherosclerotic progression, particularly among HoFH patients [28]. In the present case series, the greatest regression was seen in the patient with the highest baseline CIMT. Conceptually, lipid-rich plaques are more likely to exhibit significant regression compared to plaques with significant fibrosis and calcification.

In addition to CIMT, additional imaging techniques are available that could assist in the assessment of atherosclerotic risk in HoFH. In Patients 2 and 4, additional imaging was available that enabled assessment of total plaque area (Table 2). In both patients, while the alterations in CIMT are modest or absent, the total plaque areas regressed by a considerable amount. This underscores the value of more detailed imaging techniques to detect changes in atherosclerotic burden [29]. The present, case-based evaluation of CIMT in patients with HoFH is limited by non-standard protocols and lack of between-group comparisons.

Atherosclerotic burden in HoFH can be evaluated by multiple means, including coronary artery calcium scoring and MRI; however, ultrasound-based techniques are non-invasive, relatively cost-effective and are also not associated with exposure to ionizing radiation. Computed tomography coronary angiography, angiography and myocardial scintigraphy are most useful to evaluate vascular anatomy or myocardial perfusion [30, 31]. Although guidelines recommend regular imaging in patients with HoFH [15], the goal of such imaging is to detect coronary artery or aortic valve stenosis, rather than quantifying atherosclerotic burden.

In conclusion lomitapide reduces LDL-C levels in patients with HoFH and very severe LDL-C phenotypes, and also results in stabilisation and/or regression of CIMT, an established marker of ASCVD.

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Compliance and Ethics Guidelines. This case series was conducted as a retrospective study of normal patient care and is not subject to Institutional Review Board approval. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All of the patients provided written consent for their details to be published in the current case series. In the instances where patients died, consent was secured from the patients' estates and/or living relatives. The authors thank the patients and families.

Data Availability. The full data set is not provided as it contains identifying information, but can be secured on reasonable request from the corresponding author.

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