



# Treating homozygous familial hypercholesterolemia in a real-world setting: Experiences with lomitapide

Jeanine Roeters van Lennep, MD\*, Maurizio Averna, MD, Rodrigo Alonso, MD

*Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands (Dr Roeters van Lennep); Department of Internal Medicine and Medical Specialties, Università di Palermo, Palermo, Italy (Dr Averna); Lipid Clinic, Fundación Jiménez Díaz, Madrid, Spain (Dr Alonso); and Lipid Unit, Department of Nutrition, Clínica Las Condes, Santiago, Chile (Dr Alonso)*

## KEYWORDS:

Homozygous familial hypercholesterolemia;  
Lomitapide;  
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Treatment;  
Case study

**Abstract:** Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disease characterised by markedly elevated plasma levels of low-density lipoprotein-cholesterol (LDL-C). Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor approved as an adjunct to other lipid-lowering therapies (LLTs), with or without lipoprotein apheresis (LA), for the treatment of adult HoFH. Diet with <20% calories from fat is required. Due to a varying genetic and phenotypic profile of patients with HoFH, individual patients may respond to therapy differently; therefore examining individual cases in a ‘real-world’ setting provides valuable information on the effective day-to-day management of HoFH cases. Four HoFH cases were selected for analysis and discussion: a 20-year-old female compound heterozygote; a 62-year old female homozygote; a 42-year-old female compound heterozygote; and a 36-year-old male homozygote. Each patient was commenced on lomitapide according to the prescribed protocol and subjected to routine follow-up. All four patients experienced clinically meaningful reductions in LDL-C levels of 35–73%. Three of the patients had evidence of steatosis or mildly elevated liver function tests) before lomitapide was started, but effects of lomitapide on hepatic function were not universal. Three of the patients experienced gastrointestinal adverse events, but were managed with appropriate dietary control. Lomitapide is an effective adjunct LLT in the management of patients with HoFH, with or without LA. Real-world use of lomitapide has a side-effect profile consistent with clinical trials and one that can be managed by adherence to recommendations on dose escalation, dietary modification and dietary supplements.

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## Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disease caused most frequently by loss-of-function mutations in the low-density lipoprotein receptor

(LDL-R) gene<sup>1,2</sup> or less frequently in other genes that result in similar phenotypes (such as loss-of-function mutations in *APOB* and/or gain of function in the *PCSK9* gene, or homozygosity for mutations in *LDRAP1*).<sup>1,2</sup> HoFH is characterized by markedly and varying elevated plasma levels of low-density lipoprotein cholesterol (LDL-C).<sup>3</sup> Common (but not universal) signs of HoFH include cutaneous xanthoma and early-onset atherosclerosis.<sup>3–5</sup> In untreated patients, premature atherosclerosis develops, and patients may die prematurely.<sup>1,2</sup>

\* Corresponding author. Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands.

E-mail address: [j.roetersvanlennep@erasmusmc.nl](mailto:j.roetersvanlennep@erasmusmc.nl)

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A consensus panel of the European Atherosclerosis Society has defined treatment targets in HoFH in adults as  $<2.5$  mmol/L ( $\sim 100$  mg/dL)<sup>6</sup> and in adults with clinical cardiovascular disease (CVD) as  $<1.8$  mmol/L ( $\sim 70$  mg/dL).<sup>6</sup> Conventional treatments for HoFH have included optimizing lifestyle, such as adopting a low-cholesterol diet, and lipid-lowering therapies (LLTs), such as statins.<sup>7</sup> However, because of the lack of or deficiency in LDL-R function that characterize most HoFH patients, conventional lipid-lowering drugs that rely on upregulation of expression of intact LDL-R pathways (such as statins) do not result in adequate responses in many patients.<sup>4,7-9</sup> Therefore, HoFH treatment often includes lipoprotein apheresis (LA).<sup>8,10,11</sup>

LA can acutely reduce LDL-C levels in the blood by  $\leq 50\%$  and delay the onset of atherosclerosis.<sup>8,10,11</sup> However, the kinetics of LDL-C is such that levels rebound to baseline within 2 weeks.<sup>12</sup> Even with LA, patients can endure persistently high levels of LDL-C and remain at risk of developing premature CVD.<sup>13</sup> Given the limitations of therapies for HoFH, recent research has focussed on the development of agents that circumvent the LDL-R or disrupt the synthesis of apolipoprotein B or of the LDL precursor very low-density-lipoprotein.<sup>14,15</sup>

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor. It is approved in the United States, European Union, Canada, and Mexico as an adjunct to other LLTs (including LA) for the treatment of adult patients with HoFH.<sup>16,17</sup> MTP is a key protein in the assembly and secretion of apolipoprotein B-containing lipoproteins in the liver and intestine, and lomitapide, therefore, acts to lower LDL-C in a manner independent of LDL-R expression.<sup>18</sup>

In a pivotal phase 3 study of 29 patients with HoFH (AEGR733-005; NCT00730236), individualized dosing with lomitapide resulted in a mean 40% to 50% (depending on type of analysis used) reduction in LDL-C levels ( $P < .001$ ) at the end of the efficacy phase (week 26) and a mean  $\approx 40\%$  reduction at the conclusion of the 78-week study.<sup>19</sup> Adverse events (AEs) were primarily gastrointestinal (GI) disturbances (mild to moderate) and elevations in hepatic transaminase levels. Six patients discontinued the study: 5 due to AEs (4 GI and 1 headache), and 1 patient withdrew consent. No patient discontinued the trial due to liver toxicity.<sup>19</sup> Patients on lomitapide are required to adhere to a low-fat eating plan to minimize GI issues and set forth strict parameters for managing and monitoring hepatic transaminase levels.

In the clinical trial setting, significant efficacy was demonstrated, along with an understanding of the risk profile of lomitapide. However, little information has been presented on the benefit and/or risk profile of lomitapide and patient management in real-world clinical use. The aim of the present case series was to review four individual real-world patients with HoFH who received lomitapide to illustrate how these patients responded to therapy and to

demonstrate how side effects were managed in the clinical practice setting.

## Case reports

### Patient 1

Patient 1 is from the Netherlands and is treated at the Cardiovascular Genetics Outpatient Clinic of the Erasmus Medical Center, Rotterdam. She is a 20-year-old female with loss-of-function compound heterozygous FH caused by 2 different severe mutations in the *LDLR* gene: a 2.5-kbase deletion from exon 7 and 8 of *LDLR* (Cape Town: 2 mutations) and a 4.4-kbase duplication in exon 12 (Leiden-3 mutation; Table 1). As a result, this patient is LDL-R negative.

The patient was initially diagnosed with HoFH at age 3 years and had received treatment with conventional LLT because the age of 4. Despite maintenance therapy with oral atorvastatin (80 mg, daily) and colesevlam (1250 mg, twice daily) for 13 years, total cholesterol levels ranged from 9.9 mmol/L to peak at 18.9 mmol/L, and LDL-C levels ranged from 7.5 to 17.8 mmol/L (290–688 mg/dL). In January 2014 (at the age of 20 years), the patient was started on lomitapide (5 mg, daily). The dose was escalated stepwise to 30 mg, daily. After initiation of lomitapide (5 mg), LDL-C levels decreased from 14.11 mmol/L (566 mg/dL) to 13.8 mmol/L (534 mg/dL) in 2 months. Over the course of 5 months as lomitapide dose escalated up to 20 mg, levels of LDL-C, total cholesterol, and high-density lipoprotein-cholesterol (HDL-C) all declined. With increasing dose (30 mg), LDL-C levels were suppressed to their lowest level of 2.4 mmol/L (93 mg/dL), thereby representing an 83% reduction over 8 months (Fig. 1; Table 2).

Levels of total cholesterol were reduced from 17.3 mmol/L (669 mg/dL) before therapy to 6.1 mmol/L (236 mg/dL) over the same period (Fig. 1; Table 2).

Overall, side effects with lomitapide therapy were tolerable and primarily consisted of GI disturbances. Specifically, at the 5 mg lomitapide dose level, the patient complained of nausea and diarrhea during the initial 2 days of treatment, but not beyond that point, and intervention for GI AEs was not required. With escalation to 10 mg, side effects remained tolerable if dietary advice was adhered (diet with  $<20\%$  energy from fat) to, and the patient ate regularly. Further escalation to 20 mg saw the return of diarrhoea, some abdominal pain and stomach “rumbings.” However, the patient noted that these GI symptoms were lessened if she ate every 2 hours. Initially, she did not have additional side effects after dose escalation to 30 mg. However, after 3 weeks, dose was reduced back to 20 mg because of stomach discomfort, diarrhoea, and fatigue. After returning to the 20 mg dose, the patient felt better and did not have any further problems with side effects as long

**Table 1** Baseline characteristics of the 4 cases

Patient	Age, y/sex	BMI, kg/m <sup>2</sup>	Prelomitapide LDL-C level, mmol/L (mg/dL)*	Mutation in <i>LDLR</i> gene	
				Allele 1	Allele 2
1	20/F	24.9	14.11 (546)	2.5-kb deletion in exons 7 and 8	4.4-kb duplication in exon 12
2	62/F	26.8	10.35 (400)	16-kb deletion in exons 7 to 15	16-kb deletion in exons 7 to 15
3	42/F	35.0	7.16 (277)	5-kb deletion in exons 13 to 15	2390-?-2583+?del
4	36/M	22.4	7.3 (282)	G-A substitution at base 1646	G-A substitution at base 1646

BMI, body mass index; F, female; LDL-C, low-density lipoprotein cholesterol; M, male.

\*Not an untreated value due to background therapy.

as she adhered to the prescribed diet (<20% calories from fat). The patient did not experience any instances of elevated transaminases at any dose of the drug.

This patient continues to be monitored every 3 months for LDL-C and LFTs.

## Patient 2

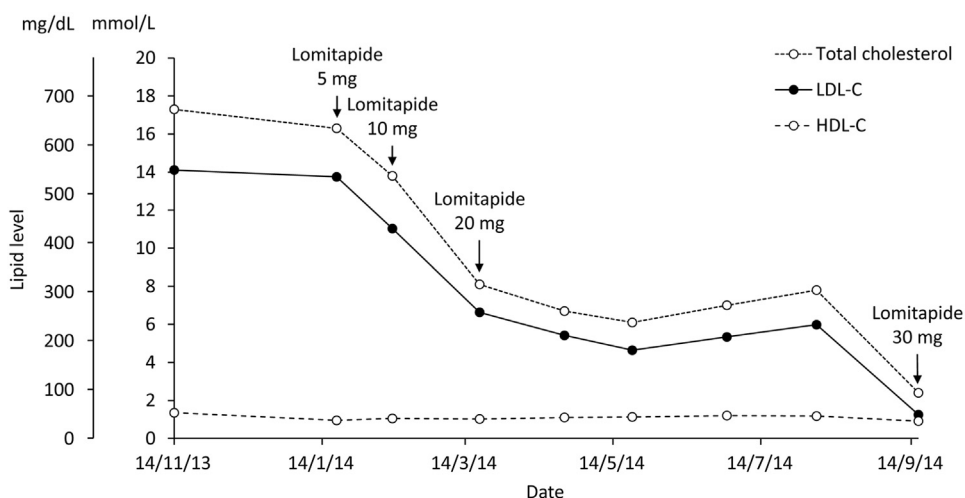
Patient 2 is also from the Netherlands and treated at the Cardiovascular Genetics Outpatient Clinic of the Erasmus Medical Center, Rotterdam. She is a 62-year-old woman with a homozygous phenotype resulting from a loss-of-function mutation in the *LDLR* (HAARLEM-1). The patient was initially diagnosed in 2014 after presentation with peak LDL-C levels of 12.9 mmol/L (499 mg/dL) and total cholesterol of 15.0 mmol/L (580 mg/dL; Table 1). She had undergone percutaneous coronary intervention and had 4 stents implanted in 2008. In 2010, she was diagnosed with type-2 diabetes mellitus. In the following 3 years, she experienced 2 episodes of statin-induced rhabdomyolysis.

In February 2014, the patient was determined to be a candidate for lomitapide therapy with the diagnosis of HoFH on clinical grounds only as genetic testing was not

performed. Ultrasound and FibroScan procedures before lomitapide initiation revealed moderate hepatic steatosis. A hepatologist was consulted to determine if a liver biopsy was warranted and whether these findings revealed a contraindication for starting lomitapide treatment. The hepatologist advised that with the established high sensitivity of ultrasound, there would be no point in conducting a liver biopsy, especially as biopsies are prone to sample error. The combination of normal levels of aspartate transaminase (AST) and alanine transaminase (ALT) and normal Fibroscan on the one side and, the elevated risk of CVD in this patient (evidenced by established CVD, diabetes, and extremely high LDL-C levels) on the other, tipped the risk-benefit balance in favor of commencing lomitapide.

Lomitapide (5 mg, p.o.) was commenced in April 2014. Levels of LDL-C, HDL-C, and total cholesterol declined within 1 month of starting treatment. LDL-C levels reached 6.7 mmol/L (259 mg/dL) by May 2014 (46% reduction; Fig. 2; Table 3).

AEs on the 5-mg dose included some loss of appetite and some stomach discomfort, but no diarrhoea and no evidence of elevated transaminase levels, and treatment did not require modification. After 2-month treatment with



**Figure 1** Patient 1: lipid profiles with escalating doses of lomitapide. Arrows represent changes in lomitapide dose according to the escalation protocol in the approved prescribing information.<sup>17</sup> HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Table 2** Patient 1: lomitapide treatment details and key lipid parameters

Week	TC, mmol/L (mg/dL)	TG, mmol/L (mg/dL)	HDL, mmol/L (mg/dL)	LDL, mmol/L (mg/dL)	ALT, U/L	Lomitapide, mg	Other LLTs	Intervention
0	17.30 (669)	1.84 (163)	1.35 (52)	14.11 (546)	17	—	Ator80	
10	16.30 (630)	0.95 (84)	0.95 (37)	13.75 (532)	22	5	Ator80	
13	13.80 (534)	0.91 (81)	1.05 (41)	11.03 (427)	20	10	Ator80	Escalate lomitapide
18	8.10 (313)	0.57 (50)	1.02 (39)	6.63 (256)	27	20	Ator80	Escalate lomitapide
23	6.70 (259)	0.46 (41)	1.10 (43)	5.42 (210)	24	20	Ator80	
27	6.10 (236)	0.41 (36)	1.13 (44)	4.64 (179)	26	20	Ator80	
33	7.00 (271)	0.987 (77)	1.20 (46)	5.34 (206)	18	20	Ator80	
38	7.80 (302)	0.63 (56)	1.18 (46)	5.98 (231)	15	20	Ator80	Escalate lomitapide
47	2.40 (93)	0.29 (26)	0.90 (35)	1.29 (50)	31	30	Ator80	
50	4.00 (155)	0.28 (25)	1.00 (39)	2.86 (111)	—	20	Ator80	Reduce lomitapide dose

ALT, alanine aminotransferase; Ator, atorvastatin (number denotes dose in mg); HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; TC, total cholesterol; TG, triglycerides.

lomitapide 5 mg in the absence of dose-limiting AEs, the lomitapide dose was escalated to 10 mg daily. Subsequently, levels of AST and ALT increased to more than 5-times the upper limit of normal ( $>5 \times \text{ULN}$ ). Therefore, according to the guidance from the lomitapide summary of product characteristics, lomitapide was temporarily withheld until the patient's liver tests normalized, which was achieved quickly. Lomitapide was restarted after 4 weeks, and the patient was monitored regularly by liver function tests (LFTs). However, after rechallenge with lomitapide 5 mg, her LDL-C decreased, but her ALT levels increased again to  $>3 \times \text{ULN}$ . Therefore, treatment with lomitapide was stopped permanently on 30 September, 2014. After discontinuation of lomitapide treatment, LFTs decreased again to normal levels.

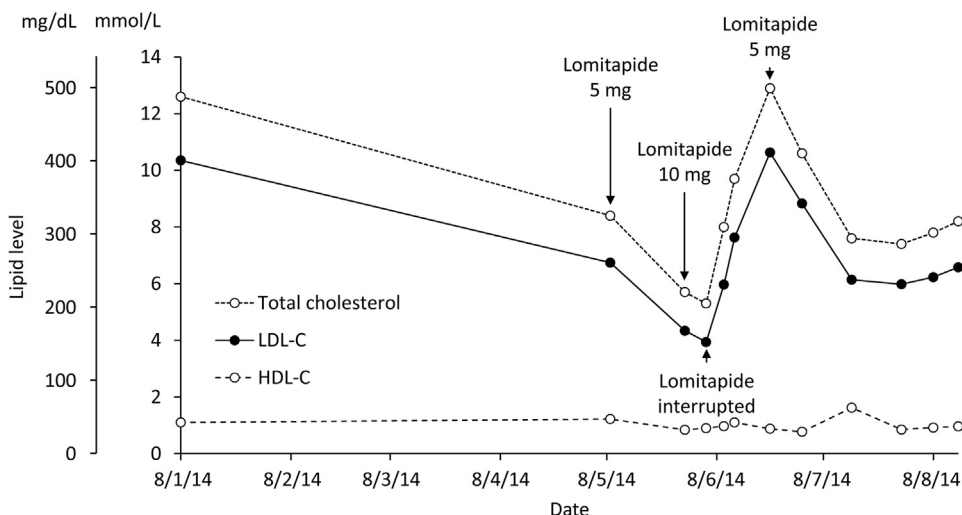
### Patient 3

Patient 3 is a 42-year-old female from Spain. She is a compound heterozygote with a change of amino acid at

position 633 (R612H) in the *LDLR* (LDL-R defective) and another copy number variation mutation 2390-?\_2583+? del (LDL-R negative).

This patient was first seen in 1979 with a total cholesterol level of 21.3 mmol/L at age 7 years. Initially, she had been treated with Plasmaclear and the bile acid sequestrant cholestyramine, and these had been moderately successful in stabilizing total cholesterol at  $\approx 13$  mmol/L and resulting in an LDL-C value of 11.4 mmol/L (previously, only total cholesterol had been monitored). With the advent of lovastatin, and then with subsequent statins, the patient was switched to a series of alternative LLTs between 1991 and 2010: lovastatin 20 to 40 mg, simvastatin 20 mg, pravastatin 20 mg, fenofibrate 250 mg, and bezafibrate 400 mg among others. Despite application of these then novel therapies, LDL-C levels continued to climb, eventually reaching 17.9 mmol/L.

During this period, the patient underwent a coronary bypass and aortic valve replacement (in 2001, aged 29 years). Between 2010 and 2013, rosuvastatin 40 mg,



**Figure 2** Patient 2: lipid profiles with escalating doses of lomitapide. Arrows represent changes in lomitapide dose according to the escalation protocol in the approved prescribing information.<sup>17</sup> HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Table 3** Patient 2: lomitapide treatment details and key lipid parameters

Week	TC, mmol/L (mg/dL)	TG, mmol/L (mg/dL)	HDL, mmol/L (mg/dL)	LDL, mmol/L (mg/dL)	ALT, U/L	Lomitapide, mg	Other LLTs	Intervention
0	12.60 (487)	3.08 (273)	1.10 (43)	10.35 (400)	16	—	None	
17	8.40 (325)	1.29 (114)	1.22 (47)	6.74 (261)		5	None	
20	5.70 (220)	0.83 (74)	0.84 (32)	4.34 (168)	143	10	None	Escalate lomitapide
21	5.30 (205)	0.94 (83)	0.90 (35)	3.94 (152)	230	—	None	Stop lomitapide
22	8.00 (309)	1.82 (161)	0.97 (38)	5.97 (231)	165	—	None	
22	9.70 (375)	2.00 (177)	1.10 (43)	7.63 (295)	138	—	None	
24	12.9 (499)	2.60 (230)	0.88 (34)	10.63 (411)	48	5	None	Restart lomitapide 5 mg
25	10.60 (410)	1.45 (128)	0.77 (30)	8.83 (341)	27	5	None	
27	7.60 (294)	0.93 (82)	1.62 (63)	6.14 (237)	56	5	None	
29	7.40 (286)	0.96 (85)	0.85 (33)	5.98 (231)	86	5	None	
30	7.80 (302)	1.13 (100)	0.92 (36)	6.23 (241)	67	5	None	
31	8.20 (317)	1.00 (89)	0.96 (37)	6.58 (254)	81	5	None	
38	7.20 (278)	1.08 (96)	0.91 (35)	—	132	5	None	Stop lomitapide
44	15.00 (580)	2.04 (181)	1.10 (43)	12.90 (500)	64	0	None	

ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; TC, total cholesterol; TG, triglycerides.

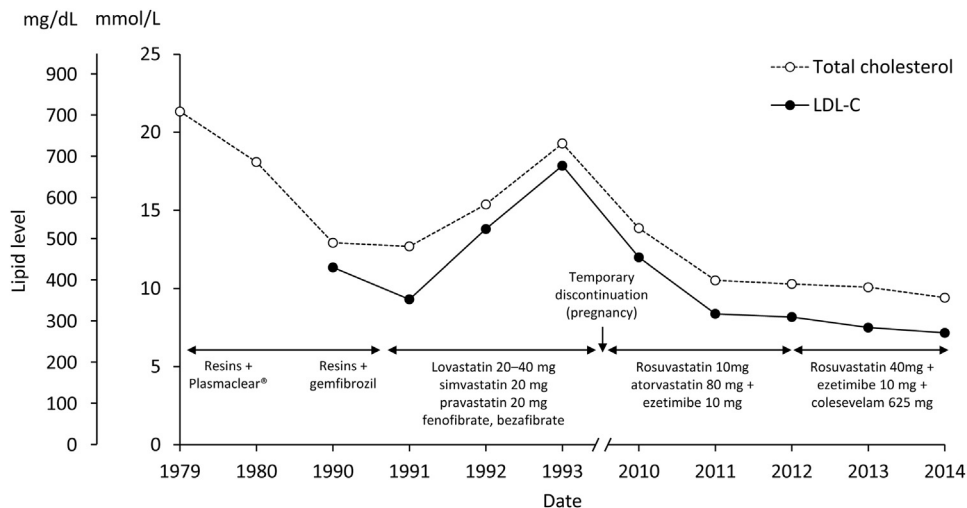
and atorvastatin 80 mg plus ezetimibe 10 mg were given. In 2014, this regimen was changed to rosuvastatin 40 mg, ezetimibe 10 mg, and colesvelam 4 × 625 mg (2.5 g/day; maximal LLT). The patient's LDL-C levels declined, but then plateaued at ~6.7 mmol/L (Fig. 3).

Beginning February 2014, the patient was started on lomitapide with maintenance of maximal background LLT (rosuvastatin 40 mg, ezetimibe 10 mg, and colesvelam 2.5 g/day). Baseline LDL-C was 7.1 mmol/L on initiation of lomitapide (5 mg, daily). Doses of lomitapide were up-titrated to 10 mg after 8 weeks on the 5-mg dose. LDL-C levels fell to 5.0 mmol/L for the 5-mg dose and to 4.7 mmol/L for the 10-mg dose (35% reduction; Fig 4; Table 4).

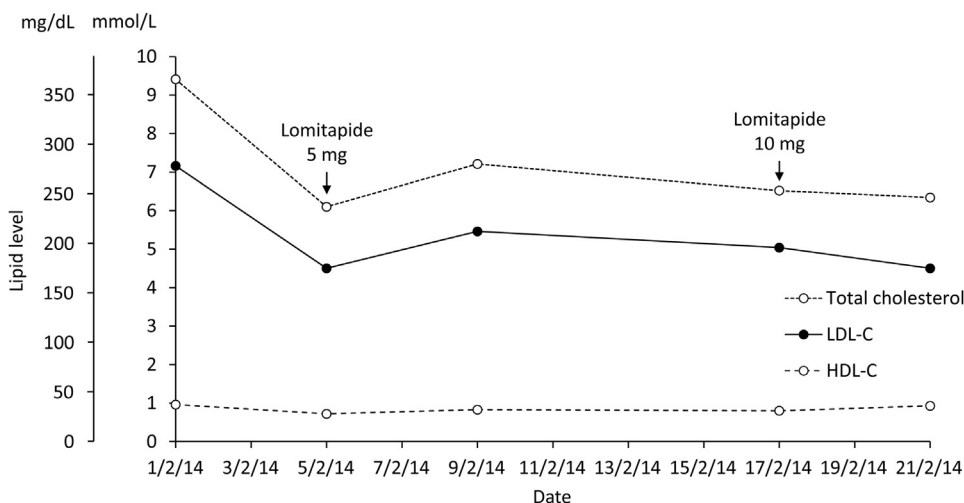
Levels of total cholesterol and triglyceride underwent similar reductions (32% and 40%, respectively). Lipoprotein (a) underwent a relatively modest reduction of 19%, and HDL-C levels remained essentially unchanged (0.8–1.0 mmol/L; Fig. 4; Table 3).

This patient had evidence of hepatic steatosis at baseline according to qualitative ultrasound. In accordance with advice for all patients receiving lomitapide, she was advised to reduce dietary intake of fat to <20%, as this regimen has been shown to minimize potential GI AEs of lomitapide. Also in accordance with the product label, the patient was advised to take supplements of vitamin E and essential fatty acids. Her weight reduced by 8.6%, and body mass index fell from 35.5 kg/m<sup>2</sup> to 32.5 kg/m<sup>2</sup>. Weight decreases are common in HoFH patients receiving lomitapide and following label-mandated dietary advice.<sup>17</sup>

ALT levels were elevated from 23 IU/L (0.7 × ULN) to 44 IU/L (1.3 × ULN) with 5-mg lomitapide, but escalation to 10 mg had no further effect. AST levels were elevated slightly from 21 IU/L (0.6 × ULN) at baseline to 36 IU/L (1 × ULN) with lomitapide 5 mg, but these resolved slightly to 31 IU/L (0.9 × ULN) on dose escalation. Levels of gamma-glutamyltransferase increased very slightly in a

**Figure 3** Patient 3: lipid profiles before lomitapide therapy. LDL-C, low-density lipoprotein cholesterol.





**Figure 4** Patient 3: lipid profiles with escalating doses of lomitapide. Arrows represent changes in lomitapide dose according to the escalation protocol in the approved prescribing information.<sup>17</sup> HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

dose-dependent manner, and vitamin-E levels were increased slightly from 28.5  $\mu\text{g/mL}$  between baseline and lomitapide 10 mg.

Long-term monitoring of this patient will be conducted using liver ultrasound every 6 months. LFT and lipid profile will be determined every month until lomitapide dose is stable. Then, analysis will be performed every 3 months. In case an increase in transaminases is observed, an evaluation by hepatologist will be considered.

The modest increase in transaminase levels were not considered a cause of concern, and the patient remains on therapy with lomitapide (7 months at the time of writing).

#### Patient 4

Patient 4 is a 36-year-old man from Italy with a homozygous c.1646G>A substitution in exon 11 of the *LDLR* (with no residual LDL-R functionality [LDL-R negative]). The patient had been treated with LA plus LLT (simvastatin 60 mg) since the age of 9 years. Ezetimibe was added when it became available in Italy (2004–2005). He was also receiving metoprolol 50 mg, twice daily and acenocumarole and lanzoprazole (both 15 mg/day). The

patient abstained from alcohol and smoking, and had a body mass index of 22.4  $\text{kg/m}^2$ .

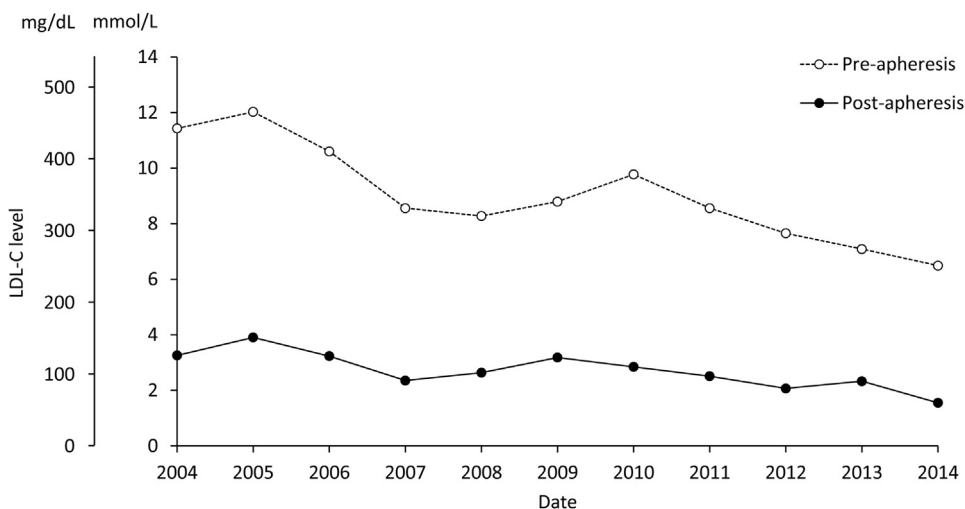
Between December 2004 and January 2005 (age, 26 years), the patient underwent coronary angiography followed by 2 coronary artery bypass grafts and mechanical aortic valve replacement. The liver showed some signs of loss of elasticity (7.5 kPa on FibroScan), but magnetic resonance imaging ruled out the excess hepatic fat. Over a 10-year period, the LA regimen plus simvastatin and ezetimibe lowered LDL-C to 2.5 to 4.0 mmol/L (immediate post-LA readings), but LDL rebound kinetics meant that LDL-C exposure remained high (Fig. 5).

Although this patient was satisfied with his LA plus LLT treatment regimen, in March 2014, lomitapide became available in his home region. Encouraged by the outcomes observed in 2 local HoFH patients receiving lomitapide who were able to stop LA (because of attainment of LDL-C levels <2.5 mmol/L), patient 4 requested the drug. Lomitapide was administered according to the approved regimen, commencing at a dose of 5 mg daily. LA was unchanged, and simvastatin was maintained at 60 mg, and ezetimibe at 10 mg. Lomitapide was up-titrated to 10 mg 2 weeks later. The authors note that in the lomitapide

**Table 4** Patient 3: lomitapide treatment details and key lipid parameters

Week	TC, mmol/L (mg/dL)	TG, mmol/L (mg/dL)	HDL, mmol/L (mg/dL)	LDL, mmol/L (mg/dL)	ALT, U/L	Lomitapide, mg	Other LLTs	Intervention
0	9.41 (364)	2.90 (257)	0.96 (37)	7.16 (277)	20	0	Ros40/Eze10/Ch2.5	
4	6.10 (236)	1.93 (171)	0.72 (28)	4.50 (174)	41	5	Ros40/Eze10/Ch2.5	Escalate lomitapide
8	7.21 (279)	2.00 (177)	0.83 (32)	5.46 (211)	46	5	Ros40/Eze10/Ch2.5	
16	6.52 (252)	1.47 (130)	0.80 (31)	5.04 (195)	46	10	Ros40/Eze10/Ch2.5	Escalate lomitapide
20	6.34 (245)	2.00 (177)	0.93 (36)	4.50 (174)	43	10	Ros40/Eze10/Ch2.5	

ALT, alanine aminotransferase; Ch, colesevelam (number denotes dose in g/d); Eze, ezetimibe (number denotes dose in mg); HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; Ros, rosuvastatin (number denotes dose in mg); TC, total cholesterol; TG, triglycerides.



**Figure 5** Patient 4: pre and postapheresis LDL-C levels over 10 years. LDL-C, low-density lipoprotein cholesterol.

clinical trial, 6 patients (of 23) had permanent changes to their apheresis regimen from weeks 26 to 78 and that the clinical benefit of reductions in background LLT, including apheresis, is not certain.

In accordance with the prescribing information for lomitapide, the patient was advised to adopt a low-fat diet and to take the required supplements.

In May, 6 weeks after commencing lomitapide with no effect on LDL-C, the lomitapide dose was further escalated to 20 mg, daily. Simvastatin was reduced to 40 mg according to the dosing recommendation in the lomitapide prescribing information. With this regimen, LDL-C levels were reduced by 73%, and total cholesterol by 62% (Fig. 6; Table 5).

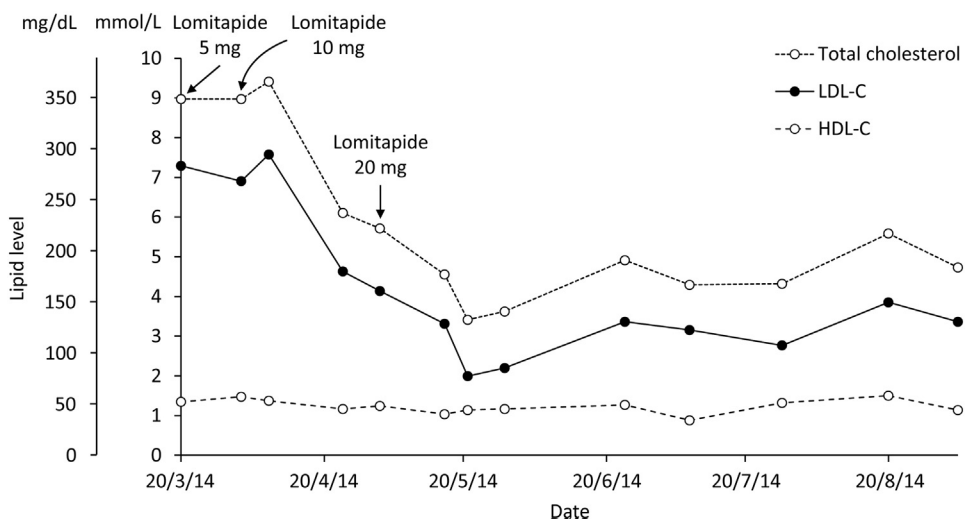
The patient experienced no GI disturbances with lomitapide dose of <10 mg; at 20 mg, he reported one episode of diarrhoea (which he attributed to over-indulgence of cake at a celebration party). The patient reported no GI

events when he adhered to the prescribed low-fat diet. Levels of AST and ALT remained stable (43–44/42–44 IU/L, with a drop to 28/19 IU/L for the 10-mg dose of lomitapide, respectively).

Patient 4 will undergo a regular monitoring schedule with particular interest in clotting parameters, liver enzymes, and bilirubin to detect signs of hepatotoxicity. Liver elastometry was reevaluated by FibroScan before escalation to lomitapide 40 mg after 6 months of treatment. Elasticity was improved (5.8 Kpa). Elastometry and magnetic resonance imaging will be conducted annually. Patient 4 remains on apheresis.

### Discussion

The present study describes the real-world use of lomitapide in 4 patients with HoFH. Before the initiation of lomitapide, limited efficacy in reducing LDL-C was



**Figure 6** Patient 4: change in lipid parameters according to lomitapide dose. Arrows represent changes in lomitapide dose according to the escalation protocol in the approved prescribing information.<sup>17</sup> HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Table 5** Patient 4: lomitapide treatment details and key lipid parameters

Week	TC, mmol/L (mg/dL)	TG, mmol/L (mg/dL)	HDL, mmol/L (mg/dL)	LDL, mmol/L (mg/dL)	ALT, U/L	Lomitapide, mg	Other LLTs	Intervention
0	9.0 (348)	0.7 (62)	1.3 (50)	7.3 (282)	42	5	Simva60/Eze10	Start lomitapide
2	9.0 (348)	1.3 (115)	1.5 (58)	6.9 (267)	19	10	Simva60/Eze10/LA	Escalate lomitapide
3	9.4 (363)	1.0 (89)	1.4 (54)	7.6 (294)	44	10	Simva60/Eze10/LA	
5	6.1 (236)	0.7 (62)	1.2 (46)	4.6 (178)	—	10	Simva60/Eze10/LA	
6	5.7 (220)	0.8 (71)	1.2 (46)	4.1 (159)	—	20	Simva60/Eze10	Escalate lomitapide
8	4.6 (178)	0.4 (35)	1.0 (39)	3.3 (128)	—	20	Simva40/Eze10/LA	Reduce Simva dose
9	3.4 (131)	0.6 (53)	1.1 (43)	2.0 (77)	31	20	Simva40/Eze10	
10	3.6 (139)	0.5 (44)	1.2 (46)	2.2 (85)	—	20	Simva40/Eze10	
14	4.9 (189)	0.6 (53)	1.3 (50)	3.4 (131)	61	20	Simva40/Eze10	
16	4.3 (166)	0.6 (53)	0.9 (35)	3.2 (124)	—	20	Simva40/Eze10/LA	
19	4.3 (166)	0.5 (44)	1.3 (50)	2.8 (108)	—	20	Simva40/Eze10/LA	
22	5.6 (217)	0.5 (44)	1.5 (58)	3.9 (151)	33	20	Simva40/Eze10	
24	4.7 (182)	0.5 (44)	1.1 (43)	3.4 (131)	—	20	Simva40/Eze10/LA	

ALT, alanine aminotransferase; Eze, ezetimibe (number denotes dose in mg); HDL, high-density lipoprotein; LA, lipoprotein apheresis; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; Simva, simvastatin (number denotes dose in mg); TC, total cholesterol; TG, triglycerides.

observed with conventional lipid-lowering medications, when used alone. Use of lomitapide in these 4 patients resulted in significant and clinically meaningful decreases in LDL-C for each patient, between 35% and 83% from baseline levels. The addition of lomitapide does require careful monitoring of transaminases for hepatic impairment. Adherence to a low-fat eating plan (<20% calories from fat) is also important to minimize GI AEs, which were the most common AEs observed in the clinical trial. Of the 4 patients, 3 remain on lomitapide treatment and 1 discontinued lomitapide treatment because of the level of ALT elevations, which resolved to normal after discontinuation.

Patient 1 exemplifies how GI side effects can be successfully managed by close adherence to a low-fat diet. This patient experienced GI side effects with the lowest dose of lomitapide (5 mg), but required dose escalation in the interests of efficacy. The dose was increased to 10 mg, which resulted in an apparent spontaneous resolution of symptoms provided the diet was followed. Further escalation to 20 mg saw the return of some GI symptoms, but with experience, the patient learned to manage GI events by ensuring that she ate every ~2 h. This case demonstrates how adaptations to the required low-fat diet can assist in the management of the GI side effects of lomitapide.

The prescribing information for lomitapide is some important dietary modifications that must be followed for patients receiving lomitapide to lessen the impact of AEs. Clinical experience (such as in patient 1) has demonstrated that adhering to these dietary modifications can have a positive impact on the tolerability, compliance, and success of lomitapide therapy. The occurrence and severity of GI AEs associated with the use of lomitapide decreases if a low-fat diet is consumed; therefore, patients should follow a diet supplying <20% of energy from fat before initiating lomitapide treatment and should continue this diet during treatment. Dietary counseling should be provided.<sup>17</sup> In clinical studies, lomitapide treatment was associated with

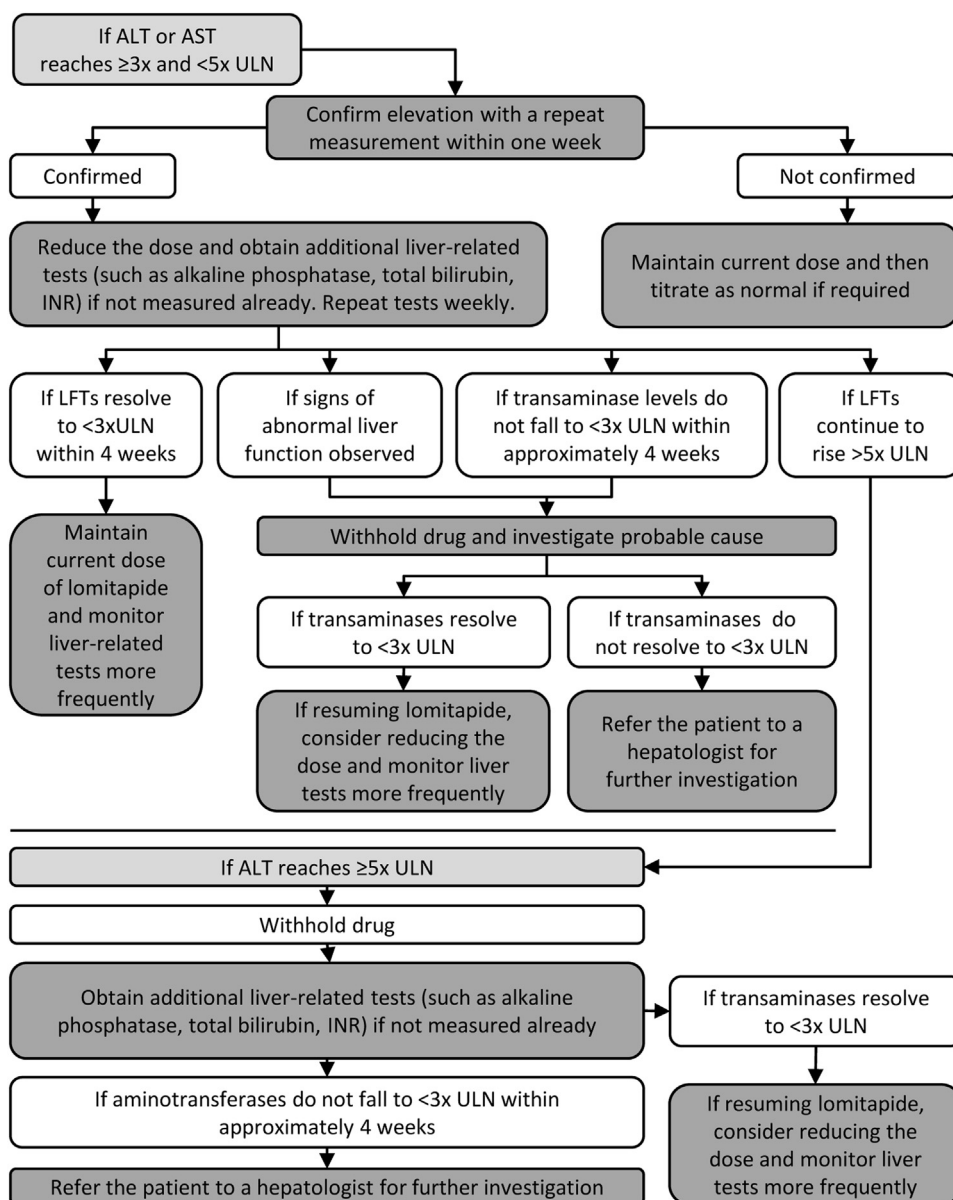
decreased levels of essential fatty acids and vitamin E. Therefore, to maintain essential fatty acids and vitamin E within normal limits, patients should be advised to take daily dietary supplements that provide 400 IU of vitamin E, as well as at least 200 mg linoleic acid, 110 mg eicosapentaenoic acid, 210 mg alpha lipoic acid, and 80 mg docosahexaenoic acid per day, throughout lomitapide treatment.<sup>17</sup>

Patient 4 highlights how lomitapide may provide benefit beyond pre-existing treatment. This patient was diagnosed with HoFH at an early age and had become accustomed to LA from the age of 9 years. The patient was, in general, tolerant to this treatment, but the “see-saw” kinetics of LDL-C for LA meant that time-averaged exposure to elevated LDL-C levels remained higher than European Atherosclerosis Society-recommended treatment targets.<sup>6</sup>

In the case of patient 4, despite the fact that he was accustomed and satisfied with LA therapy, an underlying long-term risk remained. When lomitapide was added to his pre-existing therapeutic regimen of LA, the patient’s LDL-C levels dropped 73% from baseline. Although the patient did not stop LA, the treatment interval was extended.

Because of the mechanism of action of lomitapide, accumulation of liver fat while on therapy is not unexpected.<sup>20</sup> Therefore, there is concern if a patient presents with pre-existing hepatic steatosis, which is not uncommon in patients with obesity or type II diabetes.<sup>21,22</sup> Both patients 2 and 3 presented with moderate hepatic steatosis (as evidenced from ultrasound and FibroScan), before treatment with lomitapide although other hepatic parameters were normal at baseline. In patient 3, additional hepatic complications did not arise while on therapy, and this patient continues with the treatment. This case illustrates that, although MTP inhibition causes accumulation of hepatic fat,<sup>20</sup> close monitoring of steatosis and LFTs have the potential to enable successful and well-tolerated





**Figure 7** Algorithm for managing hepatic parameters in patients receiving lomitapide. Contraindications: hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the product information,<sup>17</sup> pregnancy, moderate or severe hepatic impairment, unexplained persistent abnormal LFTs, known significant or chronic bowel disease, concomitant administration of >40 mg simvastatin, strong or moderate cytochrome P450 (CYP) 3A4 inhibitors human immunodeficiency virus protease inhibitors, diltiazem, verapamil, or dronedarone. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; LFT, liver function test; ULN, upper limit of normal.

delivery of lomitapide, but more follow-up is needed on an individual basis in our patients.

The European Summary of Product Characteristics for lomitapide suggests regular hepatic screening, including the use of imaging<sup>17</sup>; however, imaging is not specifically suggested in the US Product Information.<sup>16</sup> In our patients, FibroScan was used, which uses a transient elastography method to measure liver stiffness on the basis of transmissibility of vibrations through the liver tissue.<sup>23</sup> FibroScan is considered to be accurate, apart from in obese patients, in whom there is absorption of ultrasound by subcutaneous fat.<sup>23</sup>

Lomitapide treatment can cause elevations in ALT and AST levels; however, the extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. As directed by the lomitapide summary of product characteristics, LFTs were monitored closely throughout treatment for all patients. There were no elevations of concern in ALT/AST levels in patients 1, 3, and 4, despite moderate baseline hepatic steatosis in patient 3 and some signs of loss of hepatic elasticity in patient 4. The lomitapide summary of product characteristics recommends assessment for hepatic steatosis through evaluation of biomarkers plus imaging before

treatment with lomitapide and annually thereafter.<sup>17</sup> It also recommends this is done in consultation with a hepatologist.<sup>17</sup> In patient 2, after consultation with a hepatologist, the risk of CVD was considered to be more threatening than progression of liver steatosis. Lomitapide therapy was commenced at 5 mg, resulting in a 46% decrease in LDL-C levels. At 10-mg lomitapide, LFTs increased to  $>5\times$  ULN. Per the summary of product characteristics, lomitapide was temporarily withheld. After discontinuation, LFTs decreased rapidly, and the patient was able to start lomitapide again at 5 mg daily, which she tolerated well for an additional 14 weeks. At that time, her ALT levels again increased to  $>3\times$  ULN, and treatment with lomitapide was permanently stopped. Within 12 weeks of discontinuation, the patient's LFT values had decreased to normal levels. This patient illustrates that regular monitoring of LFTs and adherence to the suggested dose adjustment protocol enables successful use of the drug, but persistent ALT/AST elevations can resolve to normal after discontinuation of the drug. In a 2014 review, deGoma provides an overview of the management of HoFH, including a checklist for initiation of the drug and an algorithm for the management of AST/ALT elevations, similar to that shown in Figure 7.<sup>24</sup>

Given the rarity of HoFH, classic, long-term clinical study programmes will not provide meaningful population-level data on the risk–benefit profile of lomitapide, and effects on cardiovascular mortality and morbidity have not been determined. Therefore, it is important to observe the real-world use of drugs for rare diseases in individual patient cases to understand how to adapt treatment in the day-to-day clinical setting.

HoFH is not only rare but also historically difficult to treat. For 3 of the 4 HoFH cases presented here, the efficacy of lomitapide has been such that LDL-C levels have been brought under control with AEs that were either mild or manageable with adherence to dietary recommendations and protocols for monitoring and adapting to changes in hepatic parameters. The lomitapide summary of product characteristics provides an algorithm for management of LFTs, which is summarized in Figure 7, and which highlights the need to consider pre-existing hepatotoxicity and to make individualized and proportional responses to elevated LFTs.

Notably, all 4 of the patients described here had genetic confirmation of HoFH. In practice, this is not always possible, for example, because of limited access to testing. A positive genetic test for HoFH is not mandatory for the use of lomitapide.<sup>17</sup> In cases where a genetic test is either not available or reliable, diagnosis is based on clinical findings and family history.<sup>6</sup> It is noteworthy that wide variability in LDL-C levels for both treated and untreated HoFH has been described.<sup>25</sup>

In general, the clinical trial programme and the clinical experience in cases such as those described here, have shown that lomitapide is an effective LLT with and without LA when treatment is individualized to the patient's needs; however, because of the rarity of HoFH, CV outcomes have

not been assessed. Lomitapide can cause serious AEs. In accordance with the Summary of Product Characteristics, dose titration/stoppage, dietary modification, dietary supplements, and monitoring of LFTs and hepatic steatosis are required to manage potential AEs.

These real-world case studies highlight that lomitapide is an option for patients with homozygous FH who are motivated to adhere to diets and monitoring and for those treating physicians who are inspired to treat these patients for whom lipid levels are notoriously difficult to manage. Lomitapide continues to be examined as part of its pharmacovigilance programme.

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