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FULL RESEARCH PAPER
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Efficacy and safety of lomitapide in homozygous familial hypercholesterolaemia: the pan-European retrospective observational study

Laura D'Erasmo [1,*,†], Kim Steward[2†], Angelo Baldassare Cefalù[3*], Alessia Di Costanzo[1], Eric Boersma [4], Simone Bini[1], Marcello Arca[1], and Jeanine Roeters van Lennep[2]; and the Italian and European Working Group on Lomitapide in HoFH

[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Viale dell'Università 35, 00161, Rome, Italy; [2]Department of Internal Medicine, Erasmus MC, University Medical Centre Rotterdam, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands; [3]Dipartimento di Promozione Della Salute Materno Infantile, Medicina Interna e Specialistica Di Eccellenza "G. D'Alessandro" (PROMISE), Università degli Studi di Palermo, Via del Vespro 129, 90127 Palermo, Italy; and [4]Department of Cardiology, Erasmus MC, University Medical Centre Rotterdam, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands

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Aims Lomitapide is a lipid-lowering agent indicated as an adjunct therapy for adult homozygous familial hypercholesterolaemia (HoFH). This study evaluated the medium-term effectiveness and safety of lomitapide in a large cohort of HoFH patients in Europe.

Methods and results In a multicentre retrospective, observational study including 75 HoFH patients treated with lomitapide in a real-world clinical setting from 9 European countries, low-density lipoprotein cholesterol (LDL-C) changes, adverse events (AEs), and major adverse cardiovascular events (MACE) were assessed. After a median 19 months (interquartile range 11–41 months) of treatment with a mean dosage of 20 mg of lomitapide. Low-density lipoprotein cholesterol decreased by 60%, from baseline 280.5 mg/dL (191.8–405.0 mg/dL) to 121.6 mg/dL (61.0–190.5 mg/dL). At the last visit, 32.0% of patients achieved LDL-C <100 mg/dL and 18.7% <70 mg/dL. At baseline, 38 HoFH patients were receiving LDL apheresis (LA), but after initiation of lomitapide 36.8% of patients discontinued LA. During follow-up, lomitapide was permanently interrupted in 13% of patients. Gastrointestinal AEs occurred in 40% and liver transaminases increased (3–5 × upper limits of normal) in 13% of patients. Among patients with liver ultrasound evaluation ($n = 45$), a modest increase in hepatic steatosis was noted during treatment; however, liver stiffness measured by elastography in 30 of them remained within the normal range. Among HoFH patients exposed to lomitapide for at least 2 years, MACE incident rate was 7.4 per 1000 person-years in the 2 years after as compared to 21.2 per 1000 person-years before treatment with lomitapide.

Conclusion In this medium-term real-world experience, lomitapide proved to be very effective in reducing LDL-C in HoFH. Gastrointestinal AEs were common, but liver safety was reassuring with no sign of increased risk of liver fibrosis. A signal of cardiovascular protection was also observed.

Keywords Homozygous familial hypercholesterolaemia • Lomitapide • Medium-term efficacy • Medium-term safety • Atherosclerosis

Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a life-threatening genetic disorder of lipid metabolism characterized by a severe elevation of low-density lipoprotein cholesterol (LDL-C) and accelerated atherosclerosis resulting in premature cardiovascular disease and death.[1–4] It is caused by disruptive biallelic mutations in the genes that are involved in the LDL receptor functionality [*LDLR*, apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin 9 (*PCSK9*), and the LDLR adaptor protein 1 (LDLRAP1)]. These impair

* Corresponding authors. Dipartimento di Promozione Della Salute Materno Infantile, Medicina Interna e Specialistica Di Eccellenza "G. D'Alessandro" (P ROMISE), Università degli Studi di Palermo, Via del Vespro 129, 90127 Palermo Italy. Tel: +39 06 49974550, Fax: +39 06 49974551, Email: laura.derasmo@uniroma1.it (L.D.); Tel: +390916554333, Email: abaldassare.cefalu@unipa.it (A.B.C.)
†Equal contribution.

LDL particle removal from circulation resulting in severe increases in LDL-C levels.[1–5]

The extent of atherosclerosis damage and the risk of atherosclerotic cardiovascular disease events in HoFH is dependent from the life-long exposure to high LDL-C levels. The magnitude of LDL-C burden is associated with the degree of LDLR dysfunction with the greater severity in those carrying mutations of *LDLR* associated with the lack of residual receptor functionality, usually referred to as a null/null genotype.[1–5]

Previous studies have shown that reduction of LDL-C is associated with lower cardiovascular risk in HoFH, but this benefit is highly dependent on the amount of LDL-C reduction.[3–7] In a recent consensus document, the European Society of Atherosclerosis has suggested an LDL-C value <100 mg/dL in primary prevention and <70 mg/dL in secondary prevention, as therapeutic goals for HoFH.[2,6–8] Unfortunately, reducing LDL-C in HoFH is often challenging, as standard lipid-lowering therapies (LLTs) (including lipoprotein apheresis) are often ineffective in achieving LDL-C goals.[1–3]

To answer this unmet clinical need, several novel therapies have been recently developed for the treatment of HoFH.[8,9] These treatments can be classified in LDLR dependent as PCSK9 inhibitors (i.e. evolocumab and alirocumab as well as inclisiran) and LDLR independent as microsomal triglyceride transfer protein inhibitors (i.e. lomitapide), and more recently, angiopoietin-like 3 inhibitors (i.e. evinacumab).[3,8–13] Lomitapide inhibits the activity microsomal triglyceride transfer protein, which decreases liver secretion of very low-density lipoprotein (VLDL), and consequently, the production of LDL-C derived from VLDL.[11] In the Phase 3 pivotal study, the mean dose of 40 mg/day of lomitapide reduce LDL-C by ∼50%.[10] The most common adverse events (AEs) were gastrointestinal symptoms (GIs) and increases in liver transaminase elevations.[10] Based on the results reported, lomitapide has been approved in Europe, the USA, Latin America, and other regions as a lipid-lowering treatment in adults with HoFH.[14]

Subsequent data from real-world clinical practice has confirmed that lomitapide is highly efficacious and safe in subjects with HoFH.[3,12,15–19] The lipid-lowering effect was obtained with a lower dose than that used in the Phase 3 trials and was independent of *LDLR* genotype.[12] In addition, in a large proportion of lomitapide treated patients, lipoprotein apheresis was suspended or reduced in frequency.[12,19] Moreover, real-world observations confirmed that: gastrointestinal (GI) side effects were manageable with dietary modifications and/or dose adjustments. Lomitapide increases hepatic fat content with, in some cases, a concomitant increase in liver transaminases.[12]

The medium-term impact of lomitapide on liver safety still needs to be monitored. Scant information is available on how this drug affects cardiovascular risk.

We conducted a multicentre, retrospective, observational study including lipid centres treating HoFH patients with lomitapide in Europe with the aim to confirm the effectiveness and safety of lomitapide in HoFH patients managed in real-world clinical practice. As a secondary aim, we tested the hypothesis that lomitapide therapy may reduce cardiovascular risk by assessing the occurrence of major adverse cardiovascular events (MACE) during follow-up, in comparison with MACE before initiation of lomitapide therapy.

Materials and methods

Study design

The study was a multicentre, observational, retrospective, uncontrolled investigation carried out in the context of usual clinical practice and without protocol-mandated procedures. It collected data on 75 patients in Europe who were prescribed lomitapide. The Sapienza University Hospital in Rome, Italy coordinated the collection of data among Italian patients whereas the Erasmus Medical Centre in Rotterdam (The Netherlands) coordinated the collection of data on patients followed in the other European and Middle East lipid centres (Supplementary material online, *Appendix A*). A total number of 24 lipid centres agreed to participate in the study.

Patient selection

All HoFH patients known to be receiving lomitapide in Europe were considered for inclusion in this survey. The inclusion criteria were: (i) molecularly or clinically defined HoFH diagnosis,[19] (ii) age >18 years, and (iii) treatment with lomitapide for at least 1 month. Exclusion criteria were: (i) the prescription of lomitapide outside of the marketing authorization and (ii) participation in clinical trials testing investigational LLTs (defined as any drug or biologic agent that has not received market authorization in the country of participation at time of enrolment). Due to the non-interventional nature of the present study, none of enrolled patients had received any procedures outside the standard clinical care.

All identified patients agreed to be included in the survey by signing the informed consent. Informed consent was obtained before their inclusion into the study, which was carried out in accordance with the ethical standards of local institutional committees for human experimentation (Approval code #4928 and #2017-1199) and with the Helsinki Declaration of 1964, as revised in 2018.

Data collection

Physicians were asked to retrospectively retrieve demographic and clinical information from medical records. Baseline data were defined as those at the date of initiation of lomitapide, whereas last follow-up data were defined as those at the time of the last clinic visit up to 31 December 2019. The duration of follow-up was calculated as the difference between last and baseline visit.

Details of concomitant LLTs, dosages of lomitapide, and side effects at each visit were requested. Genotypes underlying HoFH were obtained from medical records and ascertained as previously reported.[19–21]

Data on MACE available at baseline and last follow-up were collected. Major adverse cardiovascular event was defined as a composite of angina, acute myocardial infarction, coronary, carotid, or peripheral stenosis >50% or revascularization and ischaemic stroke, aortic valve replacement, and cardiovascular death.[3] Major adverse cardiovascular events self-reported and/or documented by hospital admission records were also considered.[19]

Laboratory measurements

Information on locally measured plasma lipids were retrospectively retrieved by responsible physicians every 3 months for the first 3 years after baseline and every 6 months until the last visit. Data on liver function test (LFT) were available for most patients and were collected according to the same LDL-C schedule.

Efficacy assessment

The estimation of changes in plasma lipids during therapy was carried out using the following method[19]: (i) *untreated values*, corresponding to the

highest LDL-C measurement available in medical charts while the patient was not receiving any treatment; (ii) *baseline values*, corresponding to the time of beginning lomitapide; (iii) *last visit values*, corresponding to the last visit when patients were receiving lomitapide available until December 2019; and (iv) *nadir values*, estimated as the lowest LDL-C results obtained during treatment with lomitapide. The on-treatment LDL-C cholesterol ($LDL-C_{follow-up}$) was represented by the average of all LDL-C measurements available during follow-up.

Safety assessment

Adverse events were recorded throughout lomitapide treatment at the time-points of plasma lipids evaluation and were reported regardless of severity.[19] Collected events included GI events (GIs: nausea, vomiting, diarrhoea, and abdominal pain) and hepatic abnormalities (e.g. transaminases elevation). The severity of the GI side effects was rated upon clinical judgement as follows: mild, moderate, or severe. The prescribing information for lomitapide in Europe recommends frequent monitoring of hepatic enzymes and regular screening for liver steatosis and fibrosis. Investigators were asked to record laboratory values of alanine transaminase (ALT) or aspartate aminotransferase (AST) and indicate if the value was within local laboratory normal range or not. Values outside normal range were further classified indicating the level of the threshold above normal [e.g. >3 to 5 upper limits of normal (ULN), >5 to 10 ULN and >10 ULN]. Moreover, investigators were asked to retrieve all available ultrasound examinations with or without elastography performed on the dates closest to the baseline and last follow-up visit. The degree of liver steatosis was classified as mild, moderate, or severe according to the criteria of local examiners.

Statistical analysis

For descriptive statistics, continuous traits were presented as mean and standard deviation or as median and interquartile range (IQR) as appropriate.[3,12,19,21] Categorical traits were shown as number and proportion. Comparisons were carried out by Mann–Whitney for not-normally distributed and Student's *t*-test for normally distributed variables. For differences between categorical traits, *P*-value was calculated by χ^2 or by Fisher's exact test as appropriate.[3,12,19,21] Paired *t-test* was used to evaluate the difference between untreated, lowest, and last visit total and LDL-C as well as LDL-C burden pre- vs. on-treatment. Linear regression with enter method was used to evaluate the association between the variables.[3,12,19,21] Values that were not normally distributed were *log*-transformed before entering the model.

The incidence rates for MACE were calculated and expressed as number of events per 1000 patient-years.[3,19] We compared the number of MACE occurring during the 2-year interval prior to starting lomitapide, to that after initiation of lomitapide in patients who had been exposed to lomitapide for at least 24 months.[21] An exact McNemar's test (i.e. inequality test for two correlated proportions) was used to determine if there was a statistically significant difference in the proportion of subjects with MACE pre- and post-treatment with lomitapide.[22]

Statistical analyses were performed using the IBM Statistical Package for Social Sciences (IBM SPSS, version 25.0, Inc. Chicago, IL, USA). A *P*-value <0.05 was considered statistically significant.

Results

Table 1 summarizes the baseline characteristics of the 75 HoFH patients included in the study. Patients were middle aged [median age 44 (IQR 30.0–55.2) years] and almost equally distributed between sex; 80% were Caucasians and 68% were presenting tendon xanthomas. In 5 HoFH patients (6.6%), the diagnosis was based on clinical criteria, while in 64 (85.3%) was confirmed by molecular analysis. Among the 64 patients with available genetic data, 37 (57.8%) were carrying biallelic mutations in the LDLR (18 null/null, 4 null/defective, and 15 defective/defective). Eighteen patients (28.1%) were carriers of LDLR variants of uncertain significance for which the functional effect could not be determined. Their genotype was defined as Unclassified. Nine patients (13.8%) were carrying mutations in LDLRAP1 and therefore classified as affected by autosomal recessive hypercholesterolaemia. None had mutation in APOB or PCSK9. Finally, for six patients, the information on the molecular diagnosis was completely missing and these were classified as Unknown.

At baseline, 45 patients (60%) reported history of MACE. Despite patients were receiving multiple LLT including statins (89.3%), ezetimibe (84.0%), PCSK9 inhibitors (13.3%), and lipoprotein apheresis (50.7%), baseline total cholesterol and LDL-C levels remained markedly elevated [351.0 (257.0–486.0) mg/dL and 280.5 (191.8–405.0) mg/dL, respectively].

Low-density lipoprotein cholesterol lowering effect of lomitapide

The median duration of follow-up in the whole cohort of 75 HoFH patients was 19 months (IQR 11–41). Immediately after the addition of lomitapide (3 months), there was a drop of 40% in LDL-C to a median value of 151 mg/dL (*Figure 1A and B*). At the 24-month time-point, a further LDL-C decrease was observed, thus bringing the median percent reduction of LDL-C to about 56% (IQR 1.3–91.8), At this time point, the mean daily dose of lomitapide was 20.3 ± 14.1 mg/day (median 20, IQR 10.0–25.0 mg/day). Consistently with these results, the 5 years' LDL-C percent reduction was 64.7% (IQR 52.2–79.9) with an absolute reduction of 168 mg/dL from baselines values (mean daily dose of lomitapide of 33.7 ± 15.9 mg/day). It is important to note that the LDL-C lowering efficacy of lomitapide persisted up to 9 years (*Figure 1*). Indeed, the four patients with the longest follow-up (about 9 years) experienced a median percent LDL-C reduction of 59.6% (IQR 10.2–69.8) using a mean dose of 40.0 ± 16.3 mg/day.

Moreover, the benefit of lomitapide was also extended to plasma total cholesterol and triglycerides where values decreased by 35.1% and 15.8% after 3 months, and by about 53.7% and 38% after 24 months of treatment. Conversely, no changes were observed in high-density lipoprotein cholesterol (Supplementary material online, *Table S1*).

Individual LDL-C nadir percent reductions from baseline are reported in the Supplementary material online, *Figure S1*. The median nadir percent LDL-C reduction in LDL-C was 63.2% (IQR 44.1–79.7) with an absolute reduction in LDL-C levels from baseline of 179.8 mg/dL. However, these results were not homogeneous among HoFH patients (Supplementary material online, *Figure S2*). In the attempt to understand if this variability could be explained by variances in the molecular defects, we did not observe differences among genotypes (*Figure 2*). This finding confirms that lomitapide works irrespectively of residual LDLR activity and that the differences in the response to the drug must be sought elsewhere. Results of the linear regression analysis indicated that in a multivariate model including age at lomitapide prescription, gender, genotype, mean dose of lomitapide, duration of follow-up, and baseline LDL-C values, only the

Table 1 Baseline characteristics of HoFH patients

		Lomitapide cohort (*N* = 75)	
Demographic variables			
Age, years (IQR)		44 (30.0–55.2)	
Male, *n* (%)		37 (49.3)	
Geographic origin, *n* (%)			
European		60 (80.0)	
Other (African, Asian, African-American)		15 (20.0)	
Xanthomas, *n* (%)		51 (68.0)	
Genotype			
Clinical/unknown/unclassified, *n* (%)[a]		29 (38.6)	
Mutation type, *n* (%)			
LDLR			
Null/null, *n* (%)		18 (24.0)	
Null/defective, *n* (%)		4 (5.3)	
Defective/defective, *n* (%)		15 (20.0)	
LDLRAP1, *n* (%)		9 (12.0)	
Risk factors			
BMI, kg/m^2 (IQR)		24.5 (21.8–28.4)	
Current smoking, *n* (%)		6 (8.1)	
T2DM, *n* (%)		3 (4.0)	
Hypertension, *n* (%)		21 (28.0)	
MACE, *n* (%)		45 (60.0)[b]	
Plasma lipids	mg/dL		mmol/dL
Untreated			
Total cholesterol	613.0 (506.7–800.0)[c]		15.84 (13.1–20.7)
LDL-C[d]	540.0 (427.5–797.7)[e]		13.95 (11.1–20.6
Baseline			
Total cholesterol	351.0 (257.0–486.0)		9.07 (6.6–12.6)
LDL-C	280.5 (191.8–405.0)		7.25 (5.0–10.5)
HDL-C	42.5 (34.0–51.0)		1.1 (0.9–1.3)
Total triglycerides	98.0 (68.0–138.0)		1.11 (0.77–1.6)
ApoB[e]	195.5 (135.0–356.5)		0.004 (0.003–0.007)
Lipid-lowering therapies, *n* (%)			
None		5 (6.7)	
Statin		67 (89.3)	
Ezetimibe		63 (84.0)	
PCKS9i		10 (13.3)	
Fibrates		1 (1.3)	
Other[f]		5 (5.3)	
LA		38 (50.7)	
Weekly		14 (36.8)	
Bi-weekly		18 (47.4)	
Other[g]		5 (13.2)	

Data are represented as median (interquartile range) and number (percentage) as appropriate.
The worst lipid profile without any cholesterol lowering medication is reported as naïve values. Percentage associated with genotypes are reported on the whole cohort.
ApoB, apolipoprotein B; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IQR, interquartile range; LA, lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; *LDLRAP1*, low-density lipoprotein receptor adaptor protein 1; MACE, major atherosclerotic cardiovascular events; PCKS9i, proprotein convertase subtilisin/kexin type 9 inhibitors; T2DM, type 2 diabetes.
[a]In 5 patients, the diagnosis was based on clinical features (Clinical), in 18 patients, the mutation was classified unknown as the detected variant was of uncertain significance (Unclassified), and in 6 patients, we do not have any information on the molecular diagnosis (Unknown).
[b]For 4 patients this information was missing.
[c]For 17 patients this information was missing.
[d]For 15 patients this information was missing.
[e]For 30 patients this information was missing.
[f]Resins.
[g]LA ranging from every second day to monthly.

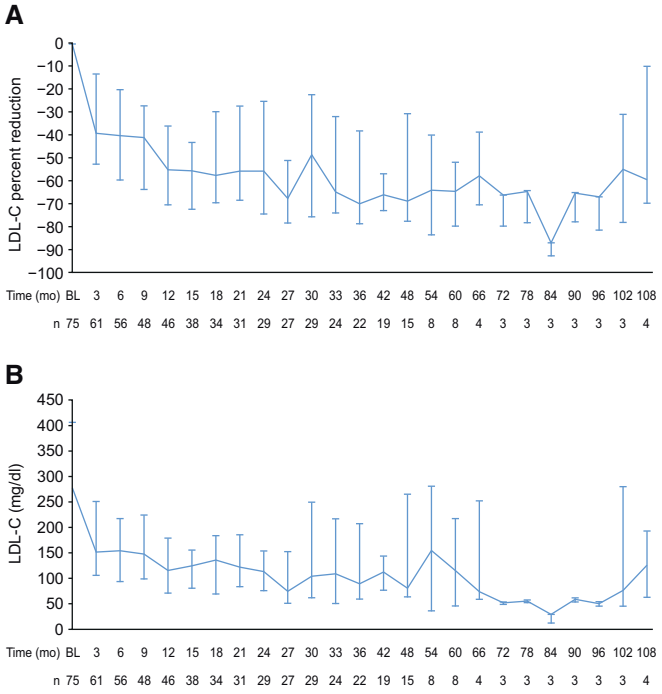

Figure 1 Median low-density lipoprotein cholesterol reduction in homozygous familial hypercholesterolaemia during follow-up. (*A*) Data are represented as median and interquartile range and reports the percent reduction at each time-point from baseline to last follow-up up to 108 months in homozygous familial hypercholesterolaemia patients receiving lomitapide. (*B*) Data are represented as median and interquartile range and represent the absolute value of low-density lipoprotein cholesterol at each time-point from baseline to last follow-up up to 108 months in homozygous familial hypercholesterolaemia patients receiving lomitapide. BL, baseline; LDL-C, low-density lipoprotein cholesterol.

duration of follow-up was directly associated with the nadir percent reduction of LDL-C (β −0.6, $P < 0.01$, data not shown) thus, suggesting that the longer the duration of treatment with lomitapide, the better the response.

When we analysed LDL-C targets' achievement, we found that the adjunct of lomitapide resulted in a reduction in LDL-C of at least 50% in 65.3% and 53.7% of HoFH, respectively at nadir and last visit, with 48% and 32% of patients exhibiting an LDL-C below 100 mg/dL (Supplementary material online, *Table S1*). These proportions, although still clinically significant, were decreased if considering the more demanding LDL-C targets of 70 mg/dL (29.3% at nadir and 18.7% at last visit) or of 55 mg/dL (25.3% at nadir and 12.0% at last visit). Notably, during follow-up no significant change in the proportion of patients taking statins, ezetimibe, and PCSK9 inhibitors was observed. More importantly, given the results obtained with the adjunct of lomitapide, LDL apheresis (LA) was stopped in 13 HoFH patients (17.3%) at nadir and in a further 14 patients (18.6%) at last follow-up (*P* McNemar < 0.001).

Safety of lomitapide

During follow-up, 10 patients (13.3%) permanently stopped lomitapide, the majority of which (70%) occurred during the first 6 months. The reasons for the discontinuation of therapy were available in six patients: one for colon cancer, four for physicians' decision (side effects/enrolment in clinical trials with other drugs for poor efficacy), and one patient moved to a country where lomitapide was not reimbursed.

The summary of AEs registered during lomitapide is shown in *Table 2*. The most frequent were represented by GI AEs, which occurred in about 40% of patients but remained stable throughout the follow-up. Diarrhoea (32.2%) and nausea (22.6%) were the most common GI AEs in the first 3 months of therapy. Most cases were reported as mild or moderate and managed by using symptomatic medication or temporary stopping or reducing lomitapide dosage. Notably, the frequency of diarrhoea and nausea showed a tendency to decrease over time, ranging between 7% and 10% at the end of the follow-up.

Between 10% and 13% of patients experienced an elevation of LFTs, which were mostly between 3 and 5 times ULN (*Table 2*). Only three patients showed a marked increase (>10 times ULN), two permanently stopped the treatment, whereas one restarted lomitapide after normalization of LFT without further safety concerns (*data not shown*). The median values of ALT and AST during the entire observational period up to 108 months remained below the thresholds of 3 times ULN. In the four patients with the longest follow-up, liver transaminases were normal at last follow-up visit (*data not shown*).

Liver ultrasound data were available for 45 patients at baseline and for 38 patients at last visit (30 subjects had both baseline and follow-up results). As showed in *Figure 3A*, there was a significant rise in the proportion of HoFH patients with a moderate liver

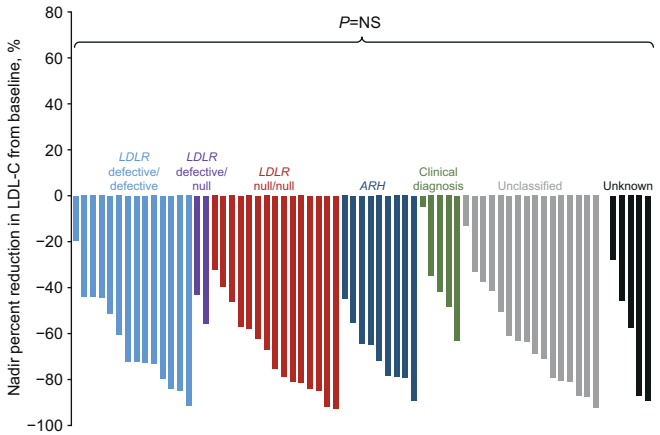

Figure 2 Nadir low-density lipoprotein cholesterol percent reduction from baseline in homozygous familial hypercholesterolaemia patients during lomitapide treatment according to mutation type. Nadir percent reduction low-density lipoprotein cholesterol from baseline values. Nadir was defined as lowest low-density lipoprotein cholesterol levels obtained with the adjunct of lomitapide. Genotypes have been defined as reported in Materials and Methods. LDL-C, low-density lipoprotein cholesterol. NS, not significant.

Table 2 Adverse events occurred during treatment with lomitapide

AE, *n* (%)	Months							
	3 (*N* = 62)	6 (*N* = 54)	9 (*N* = 48)	12 (*N* = 41)	15 (*N* = 35)	18 (*N* = 32)	21 (*N* = 28)	24 (*N* = 29)
Gastrointestinal	25 (40.3)	15 (27.8)	17 (35.4)	15 (36.6)	16 (45.7)	19 (59.4)	15 (53.6)	2 (6.9)
Nausea, *n* (%)	14 (22.6)	5 (9.3)	3 (6.3)	1 (2.4)	3 (8.6)	5 (15.6)	2 (7.1)	2 (6.9)
Vomiting, *n* (%)	0	3 (5.6)	1 (2.1)	0	0	0	1 (3.6)	0
Diarrhoea, *n* (%)	20 (32.2)	7 (13.0)	6 (12.5)	4 (9.8)	2 (5.7)	5 (15.6)	3 (10.7)	0
Abdominal pain, *n* (%)	6 (9.7)	2 (3.7)	0	1 (2.4)	3 (8.6)	5 (15.6)	3 (10.7)	0
Liver transaminases elevation	8 (12.9)	7 (13.0)	6 (12.5)	3 (7.3)	6 (17.1)	2 (6.3)	3 (10.7)	3 (10.3)
From 3 to 5 times ULN	7 (11.3)	7 (13.0)	4 (8.3)	3 (7.3)	5 (14.2)	2 (6.3)	3 (10.7)	2 (6.9)
From 5 to 10 times ULN	0	0	2 (4.2)	0	0	0	0	0
>10 ULN	1 (1.6)	0	0	0	1 (2.9)	0	0	1 (3.4)
Other[a]	1 (1.6)	0	1 (2.1)	1 (2.4)	0	1 (3.1)	0	0

Data are represented as number (percentage) and are referred to each time point during follow-up up to 24 months.
AE, adverse event; ULN, upper limit of normal.
[a]Two endocarditis, no more information available.

steatosis (5.3–17.3%, $P = 0.05$). However, none developed severe liver fat accumulation. Furthermore, elastography evaluation showed that there was no difference in hepatic stiffness between baseline and the last follow-up examination (4.6 ± 1.3 Kpa vs. 3.4 ± 2.3 Kpa, P = not significant) (*Figure 3B*). Among the 24 patients with available fibroscan data at follow-up, 7 had less and 17 had longer than 19 months of drug exposure. When we compared these groups, median values of Kpa were found to be comparable [5.1 (3.6–6.3) Kpa vs., 4.6 (4.1–5.4) Kpa, respectively]. Also, in three out of four patients with the 9-year follow-up, elastography data remained unchanged, well below the normal value <7 Kpa (for one patient data are missing).

Cardiovascular outcomes

Table 3 shows the occurrence of MACE in HoFH patients who received lomitapide for more than 24 months and had complete information on the date of event ($N = 26$). Among them, three patients experienced four events with an estimated MACE incident rate *per* 1000 person-years of 7.4%. Overall, during 2 years before initiation of lomitapide, 6 patients developed 13 events, thus generating a MACE incident rate *per* 1000 person-years of 21.2%. Despite a nominal three-fold reduction of risk of MACE after lomitapide, this difference did not reach the level of statistical significance [relative risk reduction 0.5 (95% confidence interval (IC) −0.84–0.86) and odds ratio 0.45 (95% IC 0.10–1.98)]. It is interesting to note that all these events were recurrency of MACE in those patients in whom lomitapide was

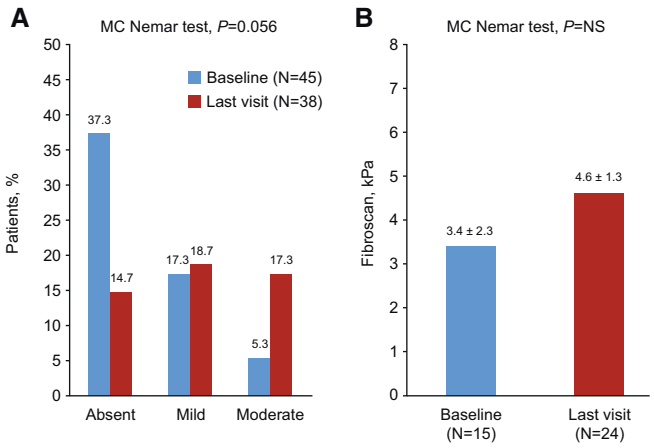

Figure 3 Changes of liver steatosis by ultrasound and elastography in homozygous familial hypercholesterolaemia patients treated with lomitapide. (*A*) Changes of liver steatosis by ultrasound measured at baseline and last visit in homozygous familial hypercholesterolaemia patients treated with lomitapide. No severe liver steatosis was reported at baseline and last visit. (*B*) Changes of liver steatosis by elastography measured at baseline and last visit in homozygous familial hypercholesterolaemia patients treated with lomitapide. NS, not significant.

prescribed late in life (mean age at baseline 56.6 years). Indeed, among the six patients with MACE 2 years before lomitapide, three experienced at least one event in the 2 years after treatment despite an on-treatment average value of LDL-C at 24 months of 70 mg/dL (data not shown).

Discussion

The Lomitapide Pan European study was established to collect data on the medium terms up to 9 years' safety and effectiveness as well as on cardiovascular outcomes in HoFH patients treated with lomitapide in the context of a real-world setting in European countries. It enrolled 75 HoFH patients with well-established diagnosis and receiving state-of-the-art treatments, including LA. Despite this, their LDL-C levels at baseline were very far from acceptable. The addition of lomitapide was associated with a reduction in LDL-C of about 56% at 24 months and, more importantly, this reduction was maintained for up to 9 years of follow-up. The average on-treatment LDL-C up to last follow-up visit was 151.9 mg/dL and 65.3% of HoFH experienced an LDL-C reduction from baseline of at least 50%. Furthermore, about half of patients reached at least one LDL-C value <100 mg/dL and one-third <70 mg/dL during the study. These LDL-C lowering effects were obtained by using a median dose of lomitapide of 20 mg/day. Moreover, although the result was not statistically significant, the treatment with lomitapide was also associated with reduced incidence of atherosclerotic cardiovascular disease.

These data are comparable with those of the Phase 3 trial in which HoFH patients receiving lomitapide showed a 50% reduction in LDL-C from baseline,[10] although with an average daily dose of lomitapide of 40 mg. A similar decrease in LDL-C was previously described in a smaller cohort of patients receiving lomitapide in Italy.[12,19] Conversely, more recent data from the LOWER registry reported in a cohort of 187 HoFH patients treated with lomitapide that LDL-C decreased by 35% at 6 months declining to 25% after 4 years of treatment, with 58.4% of patients achieving an LDL-C reduction >50% at least once.[23] However, the LOWER registry experienced a large dropout. Therefore, information on LDL-C was available for 21 patients on lomitapide at 6 months and 9 patients at 4 years. The reasons underlying the differences between our study and the LOWER Registry are not evident, but it could be due to the dissimilarities in the management of HoFH. Indeed, a higher proportion of HoFH patients were receiving high-intensity lipid-modulating therapy and lipoprotein apheresis in our study (89% and 51%, respectively) as compared to the LOWER (69% and 13%, respectively). Moreover, the mean dose of lomitapide in the Pan European study was about 15 mg/day (median 20 mg/day) compared to 10 mg/day in the LOWER. In Europe, lomitapide is predominantly dispensed by the National Health Service according to a prescription plan. Consequently, the treating physicians must frequently check their patients, and this might possibly have an impact on adherence. At the 24-month time follow-up, 10 patients (13.3%) have permanently stopped the treatment, but only 4 of them for side effects or poor efficacy. It must be noted that this proportion was slightly lower than that in the LOWER registry, where the discontinuation rate due to AEs was 23.2%. Finally, the LOWER registry included mostly patients from the USA so that their genetic background could be more heterogeneous than that of patients included in the present cohort.[23]

Consistently with previous observations, we found the LDL-C lowering efficacy of lomitapide is independent from the severity of HoFH-causing mutations being present also in carriers of null/null alleles.[12] This represents an important difference as compared to PCSK9 inhibitors alirocumab and evolocumab whose cholesterol-lowering effect depends on the residual receptor function.[24]

As expected by the mechanism of action, GIs were the most common side effects in patients receiving lomitapide.[10] In fact, lomitapide blocks the intestinal microsomal triglyceride transfer protein thus

Table 3 Occurrence of major adverse cardiovascular events (MACE) in HoFH patients who received lomitapide for more than 24 months and complete information

	HoFH ($n = 26$)
Patients with MACE 2 years before lomitapide, *n* (%)	6 (23.1)
Total MACE 2 years before lomitapide, *n* (%)	11 (31.4)
Patients with incident MACE 2 years after lomitapide (*n* (%)	3 (8.6)
Total incident MACE 2 years after lomitapide, *n* (%)	4 (11.4)
MACE incident rate [a]1000 person-months 2 years before lomitapide (%)	21.2[a]
MACE incident rate [a]1000 person-months 2 years after lomitapide (%)	7.4[a]

Data are represented as median (interquartile range) and number (percentage) as appropriate.
AoVR, aortic valve replacement; CABG, coronary artery bypass grafting; MACE, major atherosclerotic cardiovascular events; MI, myocardial infarction; PTCA, primary percutaneous transluminal coronary angioplasty.
[a]Person-month has been calculated as follows: for those without the any events in the 2 years before baseline, time for each patient were calculated as 24 months; on the contrary, for those with at least one event in the 2 years before baseline, time for each patient were calculated as the difference between the data of the first event occurred during 2 years before and date of starting lomitapide. Then, we made the sum of all these individual times before and after lomitapide (person-months variable). The MACE incident rate was estimated by dividing the cumulative number of events by the person-months variable.

impairing the intestinal fat transport and causing GI side effects.[10] In our study, about 50% of patients experienced at least one episode of GI discomfort; however, this was easily managed by withholding or reducing the drug dosage. Similar results were observed in the LOWER registry where the overall incidence of GI AEs was 46.5%.[23] In any case, the frequency of GI side effects in real-world registries appears to be much lower than that reported in the Phase 3 trials where 93% of patients experienced GI events during the efficacy phase.[10] This difference may be related to the fact that real-world patients were exposed to lower doses of lomitapide and better adherence to a low-fat diet, thus favouring greater tolerability.

In our survey, 50.6% of patients during the first 24 months reported at least one episode of elevated LFTs. However, most LFTs were between 3 and 5 times ULN, while only three patients experienced a more severe elevation (>10 times ULN). These figures appear comparable with those reported in other real-world series.[12,23] Other studies have reported increase in hepatic lipid content during treatment with lomitapide.[25] However, an additional advantage of this study is that medium-term data on structural alterations of the liver (namely fibrosis) were available through elastography measures. It is remarkable that in the group of patients with available liver safety data, no change in hepatic stiffness between baseline and the last follow-up was observed, not even in those patients with lomitapide exposure for about 9 years reporting liver imaging data. This may further indicate that the increased liver fat content observed during lomitapide treatment might not affect the risk of progression to cirrhosis over several years. Definitive investigations are needed to clarify this relevant issue.

A key strength of our study is that we present the largest number of patients with medium-term follow-up, for up to 9 years. Moreover, this is the first study providing an estimation of the cardiovascular benefit of lomitapide. In a previous modelling analysis by Leipold *et al.*,[26] authors suggested that a 38% plasma LDL-C reduction induced by lomitapide might be associated with an increase in the median life expectancy by 11.7 years and time to first MACE delayed by 6.7 years. In our cohort, there was a clear three-fold reduction in the incidence of MACE among HoFH patients who were exposed to 2 years of treatment with lomitapide compared with the 2 years before initiation of therapy. Although this difference did not reach statistical significance, probably due to the small sample size and the heterogeneity of follow-up duration, this observation suggests that lomitapide might have the ability to improve the natural history of cardiovascular complications associated with HoFH.

This study has some limitations that must be acknowledged. It is retrospective in nature and patients were not followed up according to a pre-specified protocol. Therefore, the time of data collection largely varied between centres and the management of each patient was entirely based upon the judgement of treating physicians. To mitigate the impact of these limitations, the LDL-C lowering potency of lomitapide was evaluated by reporting several indices of lomitapide effectiveness including average of all LDL-C measurements obtained during follow-up as well as the best results achieved (the nadir of LDL-C decrease). In any case, the present survey extended the evaluation of LDL-C lowering benefit of lomitapide in HoFH up to 9 years, longer than the LOWER study, which is the largest registry of lomitapide treated HoFH patients to date. Although lomitapide labelling recommends a diet supplying <20% of energy from fat to decrease the risk and severity of GIs, information about patients' dietary habits were lacking. Likewise, there was a lack of detailed information on the management of lomitapide dosages in individual patients. It must be recognized that liver steatosis was assessed only by ultrasound that is a suboptimal technique for measuring hepatic fat. However, elastography data available on 24 patients were used to assess the development of liver fibrosis which represents the most relevant clinically relevant consequences of hepatic steatosis. Moreover, no data on glucose metabolism or inflammatory parameters were available to establish any off-target effects. Nevertheless, in a recent real-world study conducted in a small subset of present cohort, we have found that high-sensitivity C-reactive protein was not altered after 3 months of lomitapide treatment, while a significant reduction was observed in a subset of patients treated for 6 months.[27] Unfortunately, also plasma ApoB measurements were missing for most of patients. Nevertheless, we believe that the significant reduction observed in the LDL-C and triglyceride levels translated into significant plasma ApoB.

Finally, HoFH patients included in this survey do not represent the totality of those receiving lomitapide in Europe. However, results on the efficacy and safety of lomitapide were superimposable to that of previous studies suggesting the reliability of our findings.

It must be recognized that Lomitapide is a quite expensive drugs accounting for an average annual cost of 180 000 euros.[19] Therefore, further studies are needed to explore in depth the pharmaco-economic aspect of this therapy thus better establishing the cost-benefit of this medication in an updated treatment algorithm of HoFH.

Conclusions

In this real-world European study, lomitapide as an adjunct to other lipid-lowering interventions was shown to be a very powerful LDL-C lowering agent in patients with HoFH for the longest follow-up period reported to date. Its beneficial effects were obtained by using a reduced mean dose of lomitapide than that used in the Phase 3 trial (20 mg vs. 40 mg) and were independent of LDLR genotype. Remarkably, in a large proportion of HoFH patients, lipoprotein apheresis treatment was no longer necessary after the addition of lomitapide. Our study provides further support for a favourable, medium-term safety profile of lomitapide in HoFH in the real world, suggesting that hepatic steatosis associated with lomitapide may not translate into increased indirect indices of liver fibrosis. Finally, the data indicate that the use of lomitapide could mitigate the elevated cardiovascular risk of HoFH patients.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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