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Individual analysis of patients with HoFH participating in a phase 3 trial with lomitapide: The Italian cohort

M. Averna [a,*], A.B. Cefalù [a], C. Stefanutti [b], S. Di Giacomo [b], C.R. Sirtori [c], G. Vigna [d]

[a] *Università di Palermo, Italy*
[b] *'Sapienza' University of Rome, Italy*
[c] *Università di Milano, Center for Dyslipidemias, Niguarda Hospital, Milano, Italy*
[d] *Università di Ferrara, Ferrara, Italy*

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Therapy

Abstract *Background and aims:* The efficacy and safety of lomitapide as adjunct treatment for adults with homozygous familial hypercholesterolaemia (HoFH) have been confirmed in a phase 3 trial. Given the small number of patients (N = 29), and variations in patient characteristics, examining individual cases provides additional details regarding patient management with lomitapide. Here, we examine the details of the Italian patient cohort in the phase 3 trial.
Methods and results: The methodology of the multinational, single-arm, open-label, 78-week, dose-escalation, phase 3 trial has been previously reported. The current report details the Italian cohort of six patients (three males, three females) based on individual patient data, individual patient histories and narratives, and by mean data ± SD.

Lomitapide was administered according to the dose-escalation protocol. At Week 78, concentrations of low-density lipoprotein-cholesterol were decreased by a mean of 42.6 ± 21.8% compared with baseline. Lomitapide was similarly well tolerated in the Italian cohort as in the entire study population. The most common adverse events were gastrointestinal symptoms. One patient showed an increase in liver transaminases >5× upper limit of normal that resolved after lomitapide treatment was reduced and maintained at a lower dose.
Conclusion: The efficacy, safety and tolerability of lomitapide demonstrated in the Italian subgroup of patients are consistent with findings in the entire study population, and illustrate the broad applicability of lomitapide therapy across genotypes and clinical phenotypes. These data also provide an insight into the management of lomitapide use in a cohort of patients within a clinical trial protocol.

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Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare, inherited disorder of cholesterol metabolism caused by two defective alleles in the low-density lipoprotein receptor (LDLR) gene or genes known to affect LDLR function. If untreated, HoFH can lead to excessively high LDL-cholesterol (LDL-C) levels, resulting in accelerated and

* Corresponding author. Department of Internal Medicine and Medical Specialties, Università di Palermo, Via del Vespro 141, I-90127 Palermo, Italy. Fax: +39 (0) 91 655 2957.
E-mail address: maurizio.averna@unipa.it (M. Averna).

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premature atherosclerosis [1,2]. There is considerable phenotypic variability in HoFH and untreated LDL-C levels can range from above 13 mmol/L to 3.9 mmol/L [3]. These phenotypic variations are driven in part by the level of residual LDL-R activity, governed by the type of mutation [4].

A recent consensus panel of the European Atherosclerosis Society (EAS) defined treatment guidelines for management of HoFH. Target LDL-C levels are <2.5 mmol/L in adults and <1.8 mmol/L in adults with clinical cardiovascular disease [4]. Effective therapies are required to meet these stringent targets; however, due to impaired LDLR activity in HoFH, standard lipid-lowering therapies (LLTs) that rely on functional LDLR (such as statins) are not sufficiently effective in HoFH.

Lomitapide is an oral small-molecule inhibitor of the microsomal triglyceride transfer protein (MTP) that has been approved as an adjunct to lipid-lowering treatment, with or without lipoprotein apheresis, in adults with HoFH [5,6]. Lomitapide reduces plasma LDL-C by directly and selectively inhibiting MTP – a protein that facilitates assembly of apolipoprotein B-containing lipoproteins in the liver and intestine – leading to reductions in lipoprotein secretion and circulating lipoprotein-borne lipids, including cholesterol and triglycerides [6].

The efficacy and safety profile of lomitapide as an adjunct treatment in adults with HoFH was confirmed in a multinational, single-arm, open-label, 78-week, phase 3 trial [7]. In that trial, lomitapide in combination with other LLTs was effective in lowering LDL-C irrespective of concomitant lipoprotein apheresis therapy [7]. Throughout the study, lomitapide exhibited a clinically manageable safety profile. The most common adverse events (AEs) were gastrointestinal (GI). Four patients (17%) had aminotransferase elevations >5× upper limit of normal (ULN), – all were managed by dose reduction or interruption [7]. In an open-label extension, lomitapide efficacy was maintained to 126 weeks (primary endpoint), and no new safety signals emerged during long-term follow-up (≤4.5 years) [8].

Due to variation in patients characteristics, including drug tolerability, the clinical trial protocol required an individualised dosing and treatment plan. Given the relatively small number of patients in the trial (N = 29) [7], it is interesting to evaluate how cases were managed, and how efficacy and safety outcomes varied according to tailored treatment, as information of this type can be used to inform treatment decisions in real-world clinical practice. We examined the efficacy and safety of lomitapide in each of the six Italian patients enrolled in the phase 3 trial; thus, providing practical insights into the management of HoFH patients with this therapy.

Patients and methods

The design of the main phase 3 trial has been reported previously [7]. Briefly, this 78-week, single-arm, dose-escalation study of lomitapide (5–60 mg) consisted of three phases: a minimum 6-week *run-in phase* followed by a 26-week *efficacy phase*, and then a 52-week *safety phase*. The primary efficacy endpoint was mean percent change from baseline in LDL-C at 26 weeks. During the efficacy phase, the dose of lomitapide was escalated based on safety/tolerability. Background LLTs (including lipoprotein apheresis) were to remain constant during the efficacy phase, but could be altered during the safety phase [7]. The individualised dose of lomitapide remained constant at the maximum tolerated dose established in the efficacy phase, unless pre-specified dosing rules mandated dose modification. At the conclusion of the safety phase, patients could enter a long-term extension. Safety endpoints included assessment of hepatic fat, as measured by nuclear magnetic resonance spectroscopy (NMRS), liver function tests, and AEs [8].

Patients were counselled by a nutritionist at their first study visit. All were provided with information on how to adopt a diet of <20% energy from fat, and patients were advised to observe associations between GI adverse events and types of foods consumed.

For confirmed elevations in alanine transaminase (ALT) or aspartate transaminase (AST) 5.0–9.9×ULN, or >100 U/L but <200 U/L above the baseline value if abnormal, the lomitapide dose was reduced, with the option to re-escalate once elevations resolved to <3×ULN [7]. If patients reached AST/ALT elevations >10×ULN, the drug was temporarily discontinued while probable causes were investigated and therapy could be re-started once the LFTs were <3×ULN.

Hepatic fat was measured non-invasively using NMRS imaging, or (if NMRS was contraindicated) computed tomography (CT) or ultrasound scanning.

The study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Approval was obtained from the ethics committee or institutional review board at each participating centre. Written informed consent was received from all patients.

Results

Patients

Three male and three female HoFH patients (diagnosed according to clinical and genetic criteria) were enrolled in four Lipid Clinics across Italy. Baseline patient characteristics, including genotypes, are summarised in Table 1. In addition to LLTs, four patients were on lipoprotein apheresis therapy conducted according to local clinical practice, patient requirements and physician discretion.

All patients were established as homozygotes or compound heterozygotes for mutations in the *LDLR* gene or genes affecting LDL-R functionality (Table 1). Patient 1, Patient 2, Patient 1 and Patient 2 were compound heterozygotes for *LDLR* mutations. Patient 3 was a true homozygote for a recessive form of familial hypercholesterolaemia (i.e., autosomal recessive hypercholestero

Table 1 Baseline characteristics of the Italian cohort in the phase 3 study of lomitapide in patients with homozygous familial hypercholesterolaemia

Patient identifier	Diagnosis of HoFH	Allelic mutations	Age/ Gender	Medical history of cardiovascular diseases	Baseline LDL-C (mg/dL)	Lipoprotein apheresis, Yes/No (Frequency)	Background lipid-lowering therapy	BMI (kg/m^2)
[a]Patient 1	Clinical, genetic	p. A512T p. G571E	19 years/ Female	Hypertension, carotid atherosclerosis determined *via* carotid ultrasound examination	181.2	Yes (every 42 days)[b]	Statin, ezetimibe	27.1
[a]Patient 2	Clinical, genetic, skin fibroblast	Del exons 13–15 p. C343R	23 years/ Male	Generalised atherosclerosis (coronary, carotid and renal arteries) since age 7 years (determined *via* coronary catheterisation). Regression of a stenosis in the anterior descending aorta while undergoing lipoprotein apheresis.	396.2	Yes (weekly)	Statin, ezetimibe	21.5
[a]Patient 3	Clinical, genetic (LDLRAP1)	c.431InsA;H114Q fs X26 c.431InsA;H114Q fs X26	45 years/ Male	Early onset arterial disease since age 8 years; transient ischaemic attack (42 years); double coronary artery bypass graft (43 years)	357.1	Yes (bi-weekly)	Statin, ezetimibe	28.7
[a]Patient 4	Clinical, genetic, skin fibroblast	p. C68R p. G571E	18 years/ Female	Absent (determined *via* coronary catheterisation)	165.7	No	Statin, ezetimibe, fenofibrate	19.3
[a]Patient 5	Clinical, genetic	p. C358R p. A378 T	19 years/ Female	Carotid atherosclerosis since age 17 years (determined *via* B-mode ultrasound)	476.8	No	Atorvastatin	20.6
[a]Patient 6	Genetic, clinical, skin fibroblast	p. C331W p. C331W	26 years/ Male	Absent (determined *via* coronary and aortic catheterisation)	216.4	Yes (weekly)	Statin, ezetimibe	21.0

LDL-C, low-density lipoprotein-cholesterol; BMI, body mass index.
[a] Patient 1 and Patient 2 were patients enrolled in the Palermo study site; Patient 3 and Patient 4 were patients enrolled in the Milan site; Patient 5 was a patient enrolled in the Ferrara site; Patient 6 was a patient enrolled in the Rome site. Patient 2 and Patient 4 were formerly treated in Rome and later moved to Palermo and Milan.
[b] This schedule may not have been effective, and therefore the efficacy of apheresis in this patient may be low. The schedule was selected according to patient preference.

laemia [ARH]) carrying the ARH7 mutation in the LDL-R adapter protein-1 (*LDLRAP1*) gene [9]. Patient 6 carried two unclassified mutations.

All six patients completed the pivotal trial according to the study protocol (Week 78). Five patients entered the extension study and were ongoing (receiving study drug and undergoing safety monitoring beyond Week 126) at the time of this analysis.

Treatment

Concomitant medications are shown in Table 1. Four patients underwent regular lipoprotein apheresis with a frequency that ranged from weekly to biweekly. One patient (Patient 1), according to stated preference and against established recommendations, received apheresis once every approximately six weeks throughout the study. Despite intensive LLT, LDL-C levels were considerably elevated at baseline (range: 4.7–12.3 mmol/L) and far above recommended EAS target levels for HoFH [4,10].

Maximum tolerated dose of lomitapide ranged from 5 mg to 60 mg (mean 40 mg) in the efficacy and safety phases. These doses were maintained in the extension phase.

Efficacy

Individual, absolute and percent changes in LDL-C levels are shown in Fig. 1A/B. At Week 26, LDL-C concentration had decreased by ≥50% compared with baseline in five patients, and by 29% in the remaining patient (Patient 5). The mean decrease for all six patients was −50.9 ± 13.0% at Week 26 (last observation carried forward), −66.3 ± 14.5% at Week 56, and −40.1 ± 27.7% at Week 78 for the five patients remaining on drug. Lomitapide efficacy was maintained in the extension study cohort (n = 5)

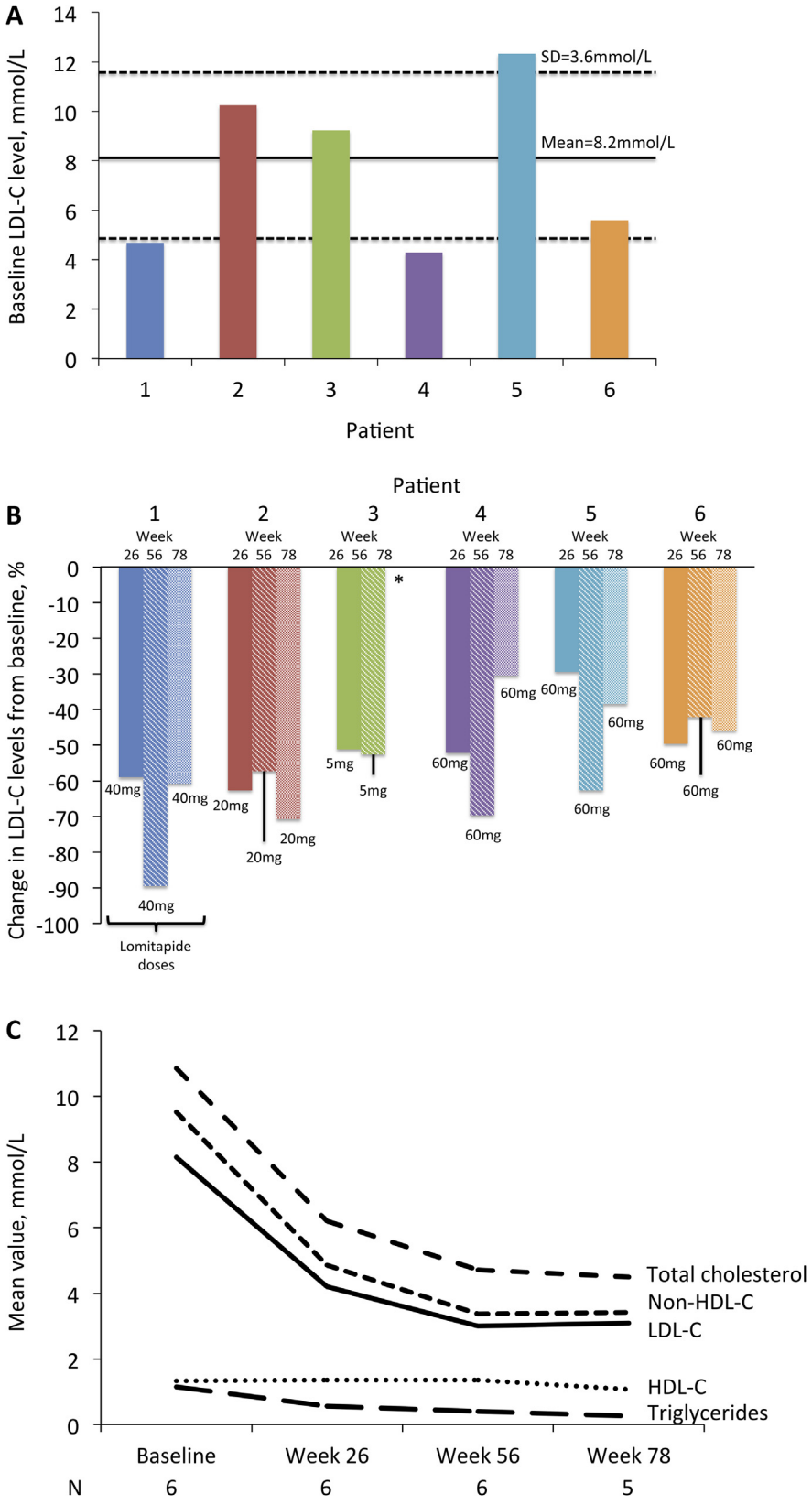


Figure 1 Effects of lomitapide on LDL-C and other lipids. (A) Individual baseline LDL-C levels. (B) Percent changes from baseline in LDL-C. (C) Mean changes in lipid parameters; *no Week 78 data.

with mean decreases of −40.8 ± 57.6% at Week 126 (n = 5).

By Week 78, concentrations of LDL-C in two patients had decreased by >60% compared with baseline (Patient 1 and 2) and by 30–46% in three patients (Patient 4, 5 and 6) (Fig. 1). At Week 126 (extension study), decreases from baseline for Patient 1, 2, 5 and 6 were sustained (−86%, −73%, −52%, and −25%, respectively). Although LDL-C values for Patient 4 showed a 31% increase from baseline at Week 126, by Week 138 this had become a 47% decrease.

Mean values for other lipid values (total cholesterol, high-density lipoprotein-cholesterol [HDL-C], triglycerides and non-HDL-C) during the 78 weeks are shown in Fig. 1C. Mean levels of non-HDL-C and total cholesterol tracked LDL-C levels closely. HDL-C levels were not affected by lomitapide, and triglyceride levels underwent a modest reduction (15%).

GI side effects

No serious GI AEs were reported for these patients during the efficacy, safety or extension phases. The most commonly reported GI events in this subgroup (diarrhoea, nausea, abdominal distension, constipation, flatulence, rectal tenesmus) were assessed to be mild-to-moderate in intensity in all but one patient. Patient 6 experienced worsening diarrhoea when the lomitapide dose was escalated to 60 mg/day at Week 14. Lomitapide was discontinued for 6 days at Day 128 due to non-serious diarrhoea (thought to be attributable to lomitapide) and restarted at 60 mg/day without further severe GI symptoms. Mean BMI of the six patients decreased from 23.0 ± 3.9 m^2/kg to 21.9 ± 1.32 m^2/kg, and was not excessively out of range for any patient [Table 1].

Although patients had been trained to limit their total fat intake to <20% of total calories, the mean percent of fat intake was above the suggested threshold (27% at baseline, 29% at Week 78). Nevertheless, the incidence and intensity of side effects decreased during the efficacy and safety phases (Fig. 2) regardless of lomitapide dose.

Hepatic side effects

Five patients experienced no elevations in LFTs of >3×ULN during either the efficacy or safety phases (Fig. 3A/B). The sixth patient (Patient 3) had elevations of ALT and AST of >5×ULN (Fig. 3C). In this patient, liver enzyme levels rose just after escalation of lomitapide dose from 5 mg to 10 mg, and reached a peak soon after starting 20 mg. The dose was reduced promptly to 10 mg and then to 5 mg. The AST and ALT levels fell to within normal limits and the patient remained on a dose of 5 mg for the duration of the study. During the long-term extension trial, four of the five patients did not experience elevations in ALT or AST ≥3×ULN. Patient 1 had an elevation between 3× and 5×ULN at Week 114, which resolved without dose adjustment.

Mean hepatic fat was 1% (range: 0.49%–2.67%) at baseline, 6.2% (3%–19%) at Week 26, 12.35% (4.3%–37.7%) at Week 56, and 10.8% (5.8%–19%) at Week 78 (Fig. 3D). For Patient 3 (who showed increased AST and ALT levels >5×ULN), hepatic fat content increased up to 37.72% at Week 56. This patient stopped treatment at Week 66 and

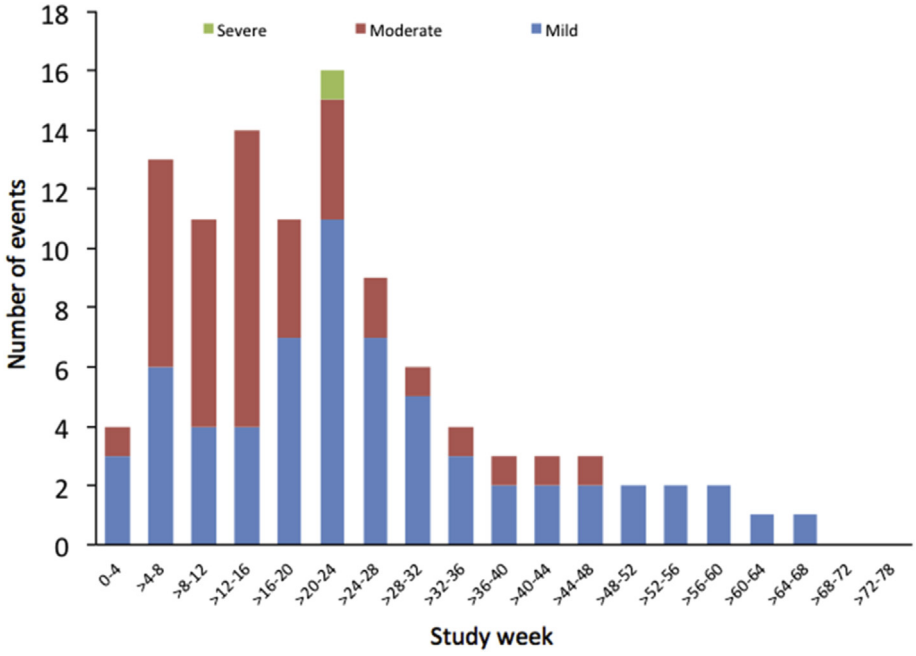
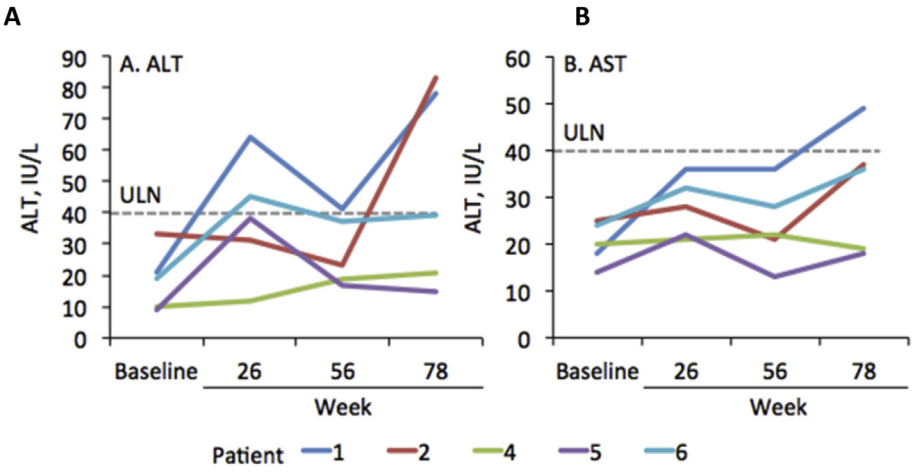
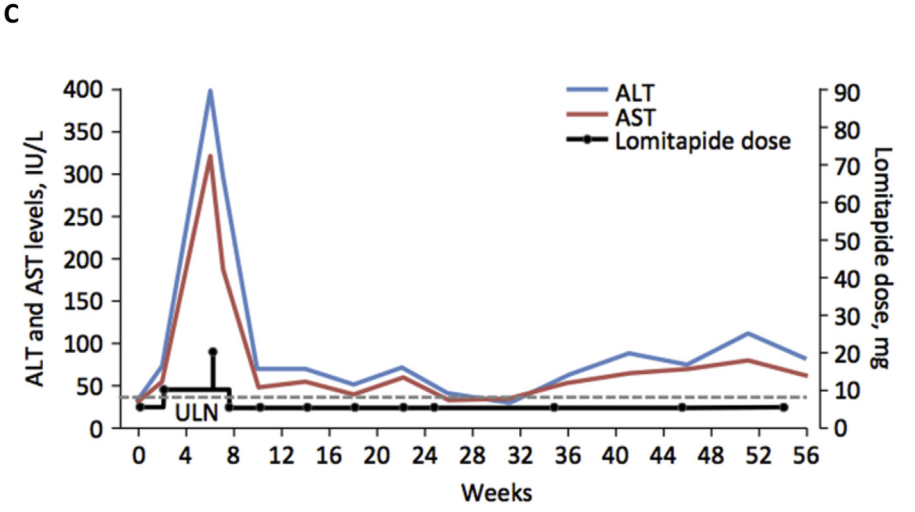
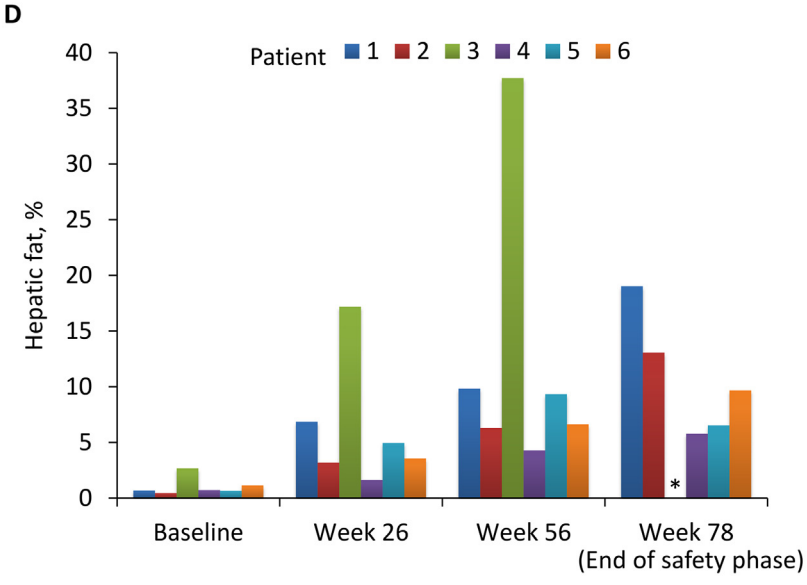


Figure 2 Number and intensity of gastrointestinal side effects.





ULN, upper limit of normal



*No Week 78 data.

Figure 3 Hepatic effects of lomitapide. (A and B) Individual transaminase levels in patients who did not meet the criteria for reduction of lomitapide dose (A: ALT and B: AST). (C) Adjustment of lomitapide dose in response to transaminase elevations >5×ULN in Patient 3. (D) Individual percent hepatic fat content (by NMRS).

did not have hepatic fat measured at Week 78 due to pain on MRI. At Week 84 (18 weeks after treatment cessation) his fat levels had decreased to 7%–15% as determined by CT scan. At Week 126, mean hepatic fat in the five patients who had continued in the extension phase was 16.2 ± 7.5% (range: 4.8%–24.7%).

Aside from Patient 3, hepatic fat continued to rise steadily in four patients (maximum 19% in Patient 1), while remaining steady for Patient 5 (Weeks 26, 56 and 78: 4.9%, 9.3%, 6.5%).

Concomitant lipoprotein apheresis therapy

Four patients (Patient 1, Patient 2, Patient 3, Patient 6) received lipoprotein apheresis at baseline. Three of these received apheresis every one to two weeks, while the fourth (Patient 1) received suboptimal apheresis therapy once every six weeks. All patients were required to be stable during the run-in period and efficacy phase. For two patients (Patient 1, Patient 2) who reached LDL-C levels <2.5 mmol/L at Weeks 26 and 36, respectively, the decision was made to stop apheresis. As the mean interval LDL-C levels were significantly lower than those before lomitapide treatment and during the efficacy phase, apheresis treatment was discontinued permanently (Fig. 4). Cardiac follow-up of these two patients confirmed no new or worsened cardiac AEs related to therapy. In addition, one patient (Patient 6) increased the time interval between apheresis treatments permanently at ~Week 34 during the safety phase. No additional modifications to apheresis treatment occurred during the extension trial.

Discussion

The Italian patients described in this analysis represent a broad range of HoFH patients based on gender, use of concomitant lipoprotein apheresis, baseline LDL-C, cardiovascular disease profile, and an assortment of underlying mutations with varying receptor functionality. By focussing on this subset of patients, we can not only learn about individual patient management in the clinical trial setting, but also understand how the varying clinical presentation and therapeutic responses that characterise HoFH can be handled on a case-by-case basis, thereby informing real-world management of the disease.

The overall efficacy and safety of lomitapide in this subgroup was consistent with that seen in the full study population [7]. At Week 26, LDL-C concentration had decreased by ≈50% compared with baseline in five patients, and by 29% in one patient (Patient 5). At Week 78, in 5 of 6 patients, LDL-C concentrations were decreased by 30% to >60% compared with baseline [7].

Responses between patients were variable, and this is to be expected for two reasons. Firstly, HoFH is a rare disease, therefore the limited patient samples introduced inherent variability that may be less evident with greater patient numbers. Secondly, as of 2011 there are upwards of 1700 identified mutations in the LDLR, 39 in LDLRAP1 and a further 163 in PCSK9 [11]. The extensive genotypic variance in HoFH is accompanied by variable phenotype, including

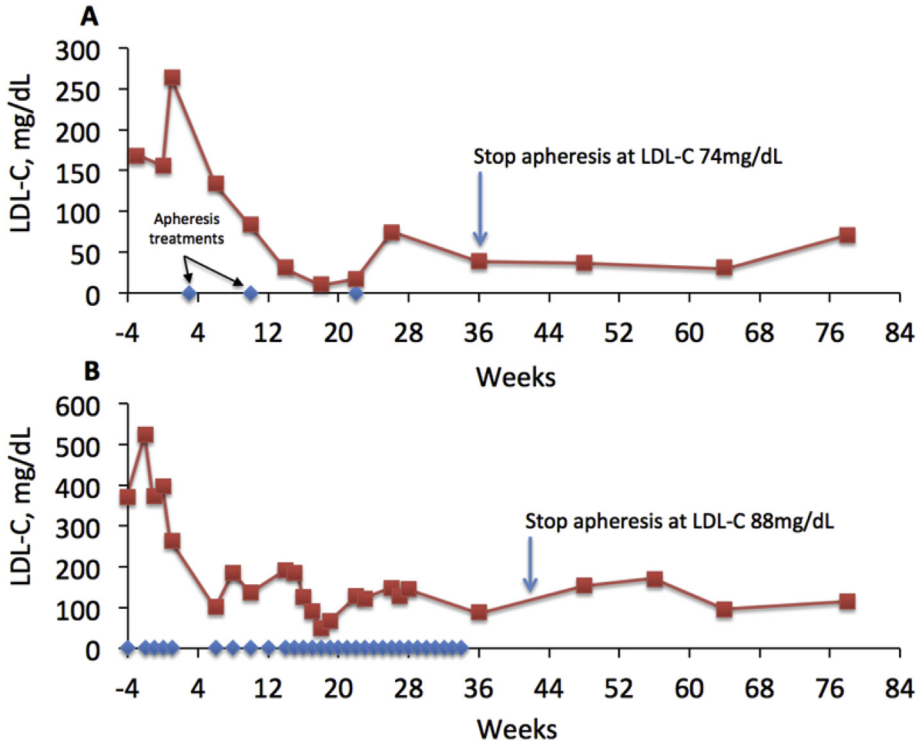


Figure 4 Changes in levels of LDL-C before and after stopping apheresis (A: Patient 1; B: Patient 2).

wide ranges of untreated LDL-C levels [4]. It is therefore reasonable that variations in response to lomitapide may be due to differences in genetic and phenotypic profile that have the potential to affect not only efficacy, but also the most tolerated dose of lomitapide for each individual as determined by the trial protocol. Notably, Patient 3, the only patient in the cohort with mutations in LDLRAP1, achieved an LDL-C reduction of 51% at Week 26 with a lomitapide dose of only 5 mg/day. Whether this response pattern is related to mutation type, is not known but it will be interesting to observe how other patients with LDLRAP1 mutations respond to lomitapide.

Analysis of the Italian cohort from the phase 3 trial indicated an upturn in mean LDL-C levels from Weeks 56–78, suggesting a decrease in efficacy. However, individual responses were highly variable and patient sample size was small. In the total trial population, mean LDL-C levels remained stable over the same period [7], which remained stable in the long-term extension phase of the trial (to Week 126) [8]. Apparent variability in the Italian cohort highlights the problems inherent in making conclusions based on mean data from small sample sizes.

Side effects associated with lomitapide were similar to those recorded in the entire study population [7]. The most common AEs were GI symptoms: diarrhoea, nausea, vomiting, dyspepsia, and abdominal pain.

The lomitapide treatment protocol is important to achieve a maximal tolerable dose, and subsequent maximal reduction in LDL-C. In particular, patients in the trial were instructed to follow a strict low-fat diet of $<$20% of the total calories from dietary fat and consumption of $\leq$1 alcoholic drink/day for women and $\leq$2 drinks/day for men; although any use of alcohol during lomitapide treatment is not recommended [6]. Only one Italian patient (Patient 3) showed an increase of transaminases $>5\times$ULN at the Week-6 evaluation, shortly after escalation of lomitapide from 10 mg to 20 mg. The percent LDL-C reduction (−9.7%) was also considerably less in this patient than that for the remainder of the cohort at Week 78. This subject's reported alcohol consumption was 7–10 drinks per week, and this was believed to be a major contributing factor in the lomitapide-induced increases in ALT and AST – the patient was not receiving any other medications extensively metabolised *via* CYP3A4. Similarly, in the full phase 3 trial population, three of the four patients who had ALT elevations $>5\times$ULN reported consumption of alcohol in quantities greater than those recommended in the protocol [7]. After an initial dose reduction back to 10 mg, and a further reduction to 5 mg, the patient in the Italian subgroup was able to remain on the lower dose of 5 mg/day for the remainder of the study.

Accumulation of liver fat is intrinsically linked to the mechanism of action of MTP inhibitors [12]. Average accumulation of hepatic fat for the Italian subgroup was consistent with that reported in the entire trial population. Notably, the same patient who had transaminase elevations $>5\times$ULN also showed a significant increase in NMRS-measured fat accumulation. After an initial rise, median hepatic fat levels appeared to increase at a slower pace. The mechanisms underlying the increase and the long-term implications of hepatic fat accumulation in patients treated with MTP inhibitors remain to be determined, and are being investigated further in the LOWER registry of patients receiving lomitapide.

Of interest, although the clinical trial protocol mandated a total fat intake $<$20% of total calories, the actual percent fat intake estimated from the diet logs was higher than advised (23%–26% for the full population; 27%–29% for the Italian cohort). These observations suggest that with continued treatment with MTP inhibition, an unknown adaptive mechanism may play a part in the improved tolerance to dietary fat.

Other concomitant LLTs (including lipoprotein apheresis) could be modified during the safety phase according to physician discretion if certain criteria were met. For example, two Italian patients discontinued apheresis treatment and one patient increased the treatment interval. The decision to stop was made by the treating physician and based on LDL-C levels being close to the EAS-recommended target [10]. Notably, Patient 2 discontinued long-term, weekly apheresis monotherapy, during which regression of a stenosis in the anterior descending aorta was evident upon coronary angiography. There was no stenosis present by June 2013. This regression was not evident in the other patient who stopped apheresis (Patient 1). Regression of stenosis with apheresis has been reported previously [13]. The benefits of apheresis addition to LDL-C lowering (including clearance of Lp(a)) [14–16] should not be underestimated. However, apheresis can be a time-consuming process and place a considerable burden on patients [17]. New therapeutic options that may allow a modified apheresis schedule may be welcomed by some patients and their families.

The current analysis illustrates the broad applicability of lomitapide therapy across varying clinical phenotypes. For example, Patient 1 and Patient 2 had different underlying genetic mutations (Table 1) and commenced with LDL-C levels of 181.2 mg/dL (4.7 mmol/L) and 396.2 mg/dL (10.2 mmol/L), respectively. Both were receiving lipoprotein apheresis and background LLT comprising a statin plus ezetimibe. Despite differing phenotypes and genotypes, both patients achieved $>$50% reduction in LDL-C by Week 26 while receiving lomitapide. Both patients stopped apheresis (Weeks 26 and 36, respectively) with no impact on lipid control. At Week 78, the LDL-C values for Patient 1 and Patient 2 were 1.8 mmol/L and 3.0 mmol/L, respectively. Notably, Patient 1 was receiving apheresis once every 42 days. Given the established rebound characteristics of LDL-C, whereby LDL-C levels return to pre-apheresis levels within 1–2 weeks [18], it is likely that the apheresis in this patient was not contributing much if anything to the observed decreases in LDL-C. Therefore, in Patient 1, decreases in LDL-C over and above statins and ezetimibe may be due solely to lomitapide. This also underscores the variability in individual response.

In conclusion, despite different clinical presentations of HoFH, the efficacy, safety and tolerability of lomitapide

demonstrated in the Italian subgroup of patients are consistent with findings in the overall phase 3 study population. LDL-C levels were significantly reduced following initiation of lomitapide therapy in all patients. This subgroup analysis highlights how individualised patient management compliant with the treatment protocol can be used to achieve meaningful and tolerable reduction in LDL-C. The efficacy and safety of lomitapide in individual patients will be informed further by data emerging from the real-world clinical use of lomitapide. To date, ~500 patients have received the drug, and lomitapide is subject to a pharmacovigilance programme that includes a registry (Lomitapide World-wide Effectiveness Registry [LOWER]), the data from which will further inform real-world clinical use of the drug [19].

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