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CASE SERIES

Is Liver Transplant Curative in Homozygous Familial Hypercholesterolemia? A Review of Nine Global Cases

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ABSTRACT

Introduction: Homozygous familial hypercholesterolemia (HoFH) is a rare, life-threatening, inherited condition characterized by extremely elevated levels of low-density lipoprotein cholesterol (LDL-C). Patients are at high risk of atherosclerotic cardiovascular disease, adverse cardiovascular events, and associated early mortality. Liver transplant is sometimes used with curative intent. The objective of the current case series was to evaluate the follow-up of a range of patients who have undergone liver transplant for the treatment of HoFH.

Methods: Patients with clinical and/or genetic diagnoses of HoFH were treated according to local practices in four units in Europe and the Middle East. All patients underwent liver transplantation. Baseline and long-term follow-up data were collected, including LDL-C levels, DNA mutations, lipid-lowering medications, and complications due to surgery and immunosuppressive therapy.

Results: Nine patients were included with up to 22 years' follow-up (mean ± SD 11.7 ± 11.7 years; range 0.5–28 years). Three of the patients died as a result of complications of transplant surgery (mortality rate 33%). Among the surviving six patients, four required continued lipid-lowering therapy (LLT) to maintain LDL-C levels and two patients show signs of increasing LDL-C levels that require management. One case (11%) required two consecutive transplants to achieve a viable graft and is awaiting a third transplant because of graft failure.

Conclusions: Liver transplant did not enable attainment of recommended LDL-C targets in most patients with HoFH, and the majority of patients still required post-transplant LLT. Liver transplant was not curative in most of the patients with HoFH followed. Guidelines suggest that transplant is a treatment of last resort if contemporary treatments are not available or possible.

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Key Summary Points

Homozygous familial hypercholesterolemia (HoFH) is a life-threatening, inherited condition that is characterized by chronic, extreme elevations of low-density lipoprotein cholesterol (LDL-C) levels

HoFH is notoriously difficult to treat. In some instances, patients have been treated with liver transplant with the aim of controlling LDL-C levels

We followed nine patients who had undergone liver transplantation for HoFH and examined long-term LDL-C outcomes

Three patients died as a direct result of the transplant procedure. Of the surviving patients, all but two required chronic lipid-lowering therapy to control LDL-C levels. Only two patients reached established LDL-C targets recommended for patients with HoFH, and both of these patients required pharmaceutical support to achieve this

Liver transplant is not universally applicable in HoFH and should only be used as a last resort when all other options have been exhausted

INTRODUCTION

Homozygous familial hypercholesterolemia (HoFH) is a genetic condition resulting from mutations in the low-density lipoprotein cholesterol (LDL-C) pathway that results in extremely high levels of circulating LDL-C [1]. This puts affected patients at elevated risk of cardiovascular (CV) mortality and morbidity. If left untreated, survival in HoFH is not expected beyond the second decade of life [1, 2].

Treatment of HoFH consists of three major modes of therapy [1]. The first of these is adoption of a healthy lifestyle along with use of statins and ezetimibe. The 2014 guidelines from Cuchel et al. specifically covered HoFH and suggested an adult target of LDL-C < 1.8 mmol/L (70 mg/dL in adults with atherosclerotic cardiovascular disease, ASCVD) and < 3.5 mmol/L (< 135 mg/dL) in children [1]. The European Atherosclerosis Society (EAS) is proposing that childhood targets should also be 70 mg/dL (1.8 mmol/L) in those at risk of CV events [3]. If patients have some residual LDL-receptor (LDL-R) activity or mutations in apolipoprotein B, then inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), such as inclisiran, evinacumab and evolocumab can be considered [4]. The microsomal triglyceride transfer protein inhibitor lomitapide has been approved for use in patients with HoFH [5], and the antisense inhibitor of apolipoprotein B synthesis mipomersen is approved in the USA [6].

A further therapy commonly applied in patients with HoFH is lipoprotein apheresis (LA). Extracorporeal removal of lipids from the blood is an effective acute strategy for lowering LDL-C. LA has been associated with positive outcomes for patients with HoFH and has become established as a mainstay of therapy [7, 8]. However, patients are exposed to high LDL-C levels between LA sessions as a result of the rapid rebound in LDL-C in the intervening days between sessions [9]. Data from Norway and the CHAIN registry have shown that CV manifestations of HoFH progress despite the application of LA [10–12]. Additionally, frequent LA sessions result in diminished quality of life (QoL) for some patients [13, 14]. LA sessions are expensive to deliver [15] and are not universally available.

In terms of a medical cure for HoFH, none exists, but since the impaired functionality of the LDL-C metabolic pathway mainly affects the liver, liver transplant was once viewed as a successful therapeutic strategy with the theoretical prospect of providing durable, long-term reduction in LDL-C levels without further therapeutic intervention [16, 17]. However,

European Atherosclerosis Society (EAS) HoFH guidelines recognize that this treatment option has obvious disadvantages due to donor scarcity, high risk of post-transplantation surgical complications and mortality, and the requirement for life-long application of immunosuppressive therapy [1]. The same immunosuppressive therapy is associated with drug-induced dyslipidemia [18, 19].

Despite historical reports of liver transplantation as a treatment for HoFH, there is a paucity of evidence on long-term survival and evolution of lipid levels of these patients beyond 3 years post-transplant [16, 17]. Here, we have reported data from patients with HoFH who underwent a therapeutic liver transplant.

METHODS

This case series includes patients with HoFH treated in three units in Europe and one in the Middle East (Spain, $n = 5$; Saudi Arabia, $n = 2$; Turkey, $n = 1$; and the Netherlands, $n = 1$). All patients were diagnosed with HoFH in childhood and treated in accordance with local standards and practices.

The data were collected from the historical patient records maintained by the treating physicians, or from the SAFEHEART registry data [20]. As such, it has not been possible to draw every desired data point from the records. Not all the data were gathered electronically, and some of the patients have been deceased for some time.

In the following commentaries, and in recognition of regional variations in clinical practice, we describe the cases by country of origin, and provide descriptive summary data on LDL-C levels.

This case series was conducted as a retrospective study of normal patient care and is not subject to institutional review board approval. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All of the patients provided written consent for their details to be published in the current case series. In the instances where patients died, consent was secured from the patients' estates and/or living relatives. The full data set is not provided as it contains identifying information. The authors thank the patients and families.

RESULTS

Data were collected from nine cases of patients with HoFH treated with therapeutic liver transplantation. Baseline data are provided in Table 1. A summary of treatment results is listed in Table 2. LDL-C values pre- and post-transplant and at last visit for all patients with follow-up data are shown in Fig. 1.

The mean age of the patients ($n = 9$) at transplantation was 10.8 years but most patients ($n = 6$) were under the age of 16 when the operation was conducted (Table 1). In patients with follow-up data ($n = 7$) mean ($\pm$ SD) LDL-C decreases achieved immediately post-transplant were 81.8% $\pm$ 9.3%, and 65.7% $\pm$ 39.5% after mean 11.7 $\pm$ 11.7 years' follow-up (Table 2), with only three patients achieving EAS LDL-C targets in the peritransplant period. Of these, only two pediatric cases (patients 6 and 9) achieved LDL-C levels < 135 mg/dL (3.5 mmol/L; EAS target for children [1]) in the peritransplant period. Only two of the surviving patients (patients 4 and 9) were at target at the time of last follow-up (Table 2). Three of the patients (33%) died of complications of surgery (Table 2), and a further patient has evidence of graft failure.

Spanish Cases

Five cases from Spain were included in the case series. In two of these cases (patients 1 and 2), the patients did not survive long enough to provide adequate follow-up LDL-C data, and data are derived from incomplete medical records and family recollections.

The first of these patients was a 14-year-old girl presenting with an LDL-C value of 909 mg/dL (23.5 mmol/L; Table 1). Statins were not available in the 1980s at the time of diagnosis. When applied, background lipid-lowering therapy (LLT) was cholestyramine. Severe aortic stenosis was noted, and the decision was made to undertake a cardiohepatic transplant. The

Table 1 Baseline characteristics of the nine patients

Patient	Country	Sex	Mutation type	Pre-Tx parameters						
				Age, years	Baseline LDL-C, mg/dL (mmol/L)[a]	Xanthomas	ASCVD	LLT	Year of Tx	Source of Tx
1	Spain	F	Compound LDLR	14	909.0 (23.5)	UNK	Severe aortic stenosis	Cholestyramine	1989	UNK
2	Spain	M	Compound LDLR	6	705.0 (18.2)	Achilles, hands	UNK	Cholestyramine	1989	UNK
3	Spain	M	Homozygous null LDLR	12	1103.0 (28.5)	Elbows	Severe aortic stenosis since age 5 years	Cholestyramine	1985	UNK
4	Spain	M	Homozygous null LDLR	18	1060.0 (27.4)	Achilles	Calcified plaque in proximal descending aorta and calcification of aortic valve annulus	Cholestyramine	1997	UNK
5	Spain	F	Homozygous null LDLR mutation	16	843.0 (21.8)	Achilles	Angina 1985, aged 4; calcified plaque in proximal descending aorta, calcific aortic atheromatosis and calcification of aortic valve annulus	Cholestyramine	1997	UNK
6	Saudi Arabia	F	Homozygous loss of function LDLR	6	544.5 (14.1)	Knees	Aortic stenosis at age 7 years	Statins	2017	Deceased donor
7	Saudi Arabia	F	Homozygous loss of function LDLR	6	706.1 (18.3)	No	No	None	2018	Deceased donor

Table 1 continued

Patient	Country	Sex	Mutation type	Pre-Tx parameters						
				Age, years	Baseline LDL-C, mg/dL (mmol/L)[a]	Xanthomas	ASCVD	LLT	Year of Tx	Source of Tx
8	Turkey	F	Homozygous LDLR	17	400.0 (10.3)	Yes	No	Statin + ezetimibe + LA	2012	Related living donor
9	The Netherlands	M	Compound null LDLR	2	970.6 (25.1)	Yes	No	Statin	2016	Living donor
Mean				10.8	804.6 (20.8)					
SD				5.9	235.9 (6.1)					
Min				2	400.0 (10.3)					
Max				18	1103.0 (28.5)					

ASCVD atherosclerotic cardiovascular disease, *F* female, *LA* lipoprotein apheresis, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *M* male, *Tx* transplant, *UNK* unknown

[a]Last LDL-C measurement available before transplant

Table 2 Treatment results in the nine patients

Patient	Post-Tx parameters						
	LDL-C after Tx, mg/dL (mmol/L)	LDL-C after follow-up, mg/dL (mmol/L)	Length of follow-up, years	Major surgical complications	Immunosuppressive therapy	LLT	Progression of ASCVD
1	N/A	N/A	N/A	Death caused by complications of transplant surgery	N/A	N/A	N/A
2	N/A	N/A	N/A	Death caused by complications of transplant surgery	N/A	N/A	N/A
3	142.0 (3.7)	132.0 (3.4)	28.0	Complications (generalized infection) of immunosuppression required to support graft	UNK	None	UNK
4	110.0 (2.8)	69.0 (1.8)	22.0	0	Tacrolimus	Statin	UNK
5	91.0 (2.4)	112.0 (2.9)	21.8	0	Tacrolimus, everolimus	Ezetimibe	UNK
6	134.2 (3.5)	184.8 (4.8)	1.6	0	Tacrolimus	Statin + ezetimibe	UNK
7	172.9 (4.5)	335.7 (8.7)	0.5	0	Tacrolimus for 5 months	None	UNK
8	135.0 (3.5)	469.0 (12.1)	5.3	0	Tacrolimus	Statin + ezetimibe	None
9	104.4 (2.7)	92.8 (2.4)	2.7	0	Tacrolimus, prednisolone	None	None
Mean[a]	127.1 (3.3)	199.3 (5.2)	11.7				
SD[a]	27.5 (0.7)	148.3 (3.8)	11.7				
Min[a]	91 (2.4)	69 (1.8)	0				
Max[a]	173 (4.5)	469 (12.1)	28				

ASCVD atherosclerotic cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *N/A* not applicable, *Tx* transplantation, *UNK* unknown

[a]In patients with follow-up data (n = 7)

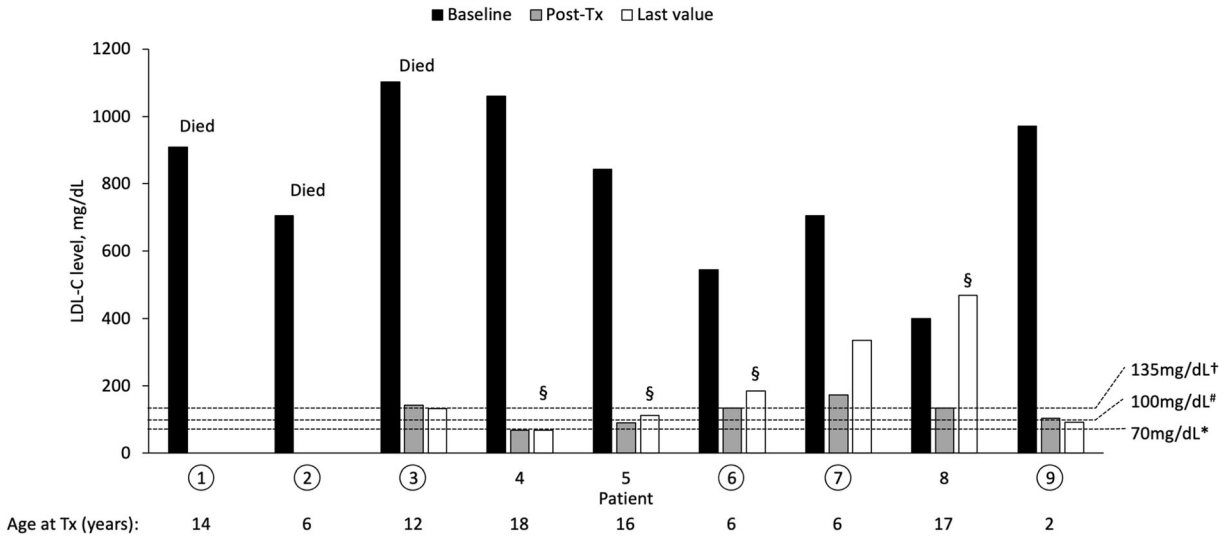

Fig. 1 LDL-C levels at baseline, nadir, and last visit for patients with follow-up data. Baseline is taken as the last LDL-C determination before liver transplantation; nadir (post-Tx) is the lowest value recorded after transplantation; circled numbers indicate pediatric patients; cause of death in patients 1 and 2 was complications of transplant surgery; cause of death in patient 3 was complications arising from immunosuppressive therapy required to support graft. *European Atherosclerosis Society (EAS) adult target for LDL-C; †EAS pediatric target for LDL-C; §follow-up value obtained while patient was receiving lipid-lowering therapy. *LDL-C* low-density lipoprotein cholesterol, *Tx* transplantation

patient died in 1989 aged 14 years as a result of surgical complications in the peritransplant period (Table 2). No LDL-C levels were available after liver transplantation.

The second fatal case, also from the 1980s, was a 6-year-old boy with HoFH and a plasma LDL-C level of 705 mg/dL (18.2 mmol/L) on cholestyramine (Table 1). CV status was unknown. The decision was taken to conduct a liver transplant in 1989. This patient also died in the peritransplant period from complications of surgery (Table 2).

A final, fatal case from Spain was a 41-year-old man with HoFH, xanthomas, and severe aortic stenosis (Table 1). At the age of 11 (1984, and before the advent of statins) the patient was treated with cholestyramine and LDL-C levels were 1103 mg/dL (28.5 mmol/L). A cardiohepatic transplant was conducted the following year (age 12), and LDL-C levels reduced to 142 mg/dL (3.7 mmol/L). Despite good clinical parameters, the patient eventually died in 2014, 29 years after the initial transplant. A year before death, LDL-C levels were recorded at 132 mg/dL (3.4 mmol/L; Table 2). The medical team determined that the patient died as a consequence of sepsis due to the chronic immunosuppressive therapy required to support the graft.

The first surviving Spanish case (patient 4) is a 40-year-old male patient (Table 1). At the age of 18, the patient had LDL-C levels of 1060 mg/dL (27.4 mmol/L). A hepatic transplant was conducted. LDL-C levels reduced to 110 mg/dL (2.8 mmol/L). At the ages of 21 and 25 years LDL-C was 132 and 165 mg/dL (4.3 mmol/L), respectively, and LLT was restarted in 2005 with atorvastatin 20 mg. LDL-C levels decreased to 99 mg/dL (2.6 mmol/L). A recent follow-up lipid screen at age 39 (21 years post-transplant and on statins) revealed an LDL-C level of 69 mg/dL (1.8 mmol/L), indicating a percentage reduction of 93.5% over that time and normalization of LDL-C levels with continued support from LLTs (Table 2). The patient continues immunosuppressive treatment with tacrolimus 2 mg/day.

The second surviving case (patient 5) is a 37-year-old woman, diagnosed with HoFH at the age of 4 years following investigation for

family history of FH (Table 1). In 1997, at the age of 16, LDL-C levels were 843 mg/dL (21.8 mmol/L). A liver transplant was conducted with an immediate second transplant due to hepatic artery thrombosis in the primary graft. In 2014 (age 33), a coronary computed tomography angiography revealed subclinical ASCVD with calcification in the aortic valve annulus, calcified aortic atheromatosis, and calcified plaques in the descending aorta. A recent lipid screen (2018, age 36, 21 years post-transplant) showed that the patient had LDL-C levels of 91 mg/dL (2.4 mmol/L; 89.2% reduction from pre-transplant values) which were achieved without application of additional chronic statin therapy. The patient had developed chronic liver disease and portal hypertension. A further lipid screen in 2019 showed LDL-C levels of 132 mg/dL (3.4 mmol/L). Lipid-lowering treatment was commenced with ezetimibe, and LDL-C levels decreased to 112 mg/dL (2.9 mmol/L). No statins were indicated because of liver failure. She continues immunosuppressive treatment with tacrolimus 2 mg/day and everolimus 1.5 mg/day (Table 2). The patient is now awaiting a third transplant despite adherence to immunosuppressive therapy. This patient was deemed at a high risk of ASCVD, which has resulted in LDL-C targets to be set at $\leq$ 70 mg/dL (1.8 mmol/L).

Saudi Arabian Cases

The two cases from Saudi Arabia are both young girls aged 7 and 6 years (Table 1). The older of the two (patient 6) was diagnosed with HoFH at the age of 3. LDL-C levels were elevated to 545 mg/dL (14.1 mmol/L). When the patient reached the age of 6 years, and with no improvement in LDL-C levels on atorvastatin 20 mg, and despite the relatively low statin dose, a deceased donor liver transplant was conducted on family request in the USA. Immunosuppressive tacrolimus was provided. In response to the transplant, the patient showed a decrease in LDL-C levels to 134 mg/dL (3.5 mmol/L; 75.4% reduction). In 2019 (age 9), the patient's LDL-C levels had increased slightly to 184 mg/dL (4.8 mmol/L), but there was no sign of liver pathology (Table 2). As the patient did not achieve acceptable LDL-C levels post transplantation, statins and ezetimibe were continued post-transplant, and the patient may still require additional pharmacotherapy to reduce LDL-C levels. Progress is being monitored.

The second case (patient 7) is a young girl diagnosed at 17 months of age with HoFH due to elevated LDL-C levels (approx. 600 mg/dL; 15.5 mmol/L) There was a history of HoFH in the family. With experience of transplantation in the USA for a nephew, the family sought transplant when the patient was 6 years old and LDL-C levels were 706 mg/dL (18.3 mmol/L; Table 1). The transplant was conducted in the USA from a deceased donor liver transplant. There were no immediate complications, and LDL-C levels had decreased to 173 mg/dL (4.5 mmol/L), albeit still above EAS target (< 135 mg/dL; 3.5 mmol/L; Table 2). A picture of chronic rejection and cytomegalovirus hepatitis developed, together with elevated liver function tests (LFTs) and increasing LDL-C levels. Tacrolimus was administered for 5 months after the transplant with eventual tapering and cessation due to issues with the liver. LDL-C levels are now in the range of 300–450 mg/dL (7.8–11.6 mmol/L), and significantly above the target levels of 135 mg/dL (3.5 mmol/L) in children.

Liver biopsy in November 2018 showed mild acute cellular rejection and mild lobular necroinflammation, but the patient was negative for significant fibrosis, or immunohistochemically determined cytomegalovirus. Another liver biopsy on 6 January 2019 showed preservation of normal liver architecture. Six portal tracts were noted with no inflammation and venulitis. While there was no loss of bile ducts, the ducts are not completely healthy. Endothelial centered xanthoma cells were evident in the hepatic artery. As a result of acute graft rejection, the patient now receives tacrolimus and mycophenolate mofetil with regular follow-up in a liver transplant clinic.

Turkish Case

The case from Turkey (patient 8) is that of a 22-year-old woman diagnosed with HoFH at the age of 3 years with elevated LDL-C (600 mg/dL) (15.5 mmol/L) and evidence of xanthomas (Table 1) with a family history of premature ASCVD.

The mainstay of therapy for the patient was LA (with statins and ezetimibe), but as this was becoming a burden for her, the option for liver transplantation was explored. There was no coronary pathology on stress test prior to the transplant. A graft was acquired from a third-degree cousin, and at the time of the transplant, the patient's LDL-C level was 400 mg/dL (10.3 mmol/L) and that of the donor was 102 mg/dL (2.6 mmol/L).

Surgery was conducted at age 17 years with no complications, and there were no sequelae of the transplantation for the following 4 years, during which no background LLT was required. Tacrolimus 1 mg/day was given to prevent graft rejection. However, 4 years after the transplantation, LDL-C levels began to increase (range 180–400 mg/dL) (4.7–10.3 mmol/L). The patient rejected LA, so ezetimibe 10 mg/day was given, which was later supplemented with atorvastatin 80 mg according to the preference of the attending physician (Table 2). Elevations in LDL-C have not been accompanied by hypothyroidism, graft rejection, or elevation in LFTs. While there has been no clinical graft failure or rejection, confirmatory liver biopsy was not conducted.

Dutch Case

The case from the Netherlands (patient 9) is that of 5-year-old boy diagnosed with HoFH at the age of 1 year, 6 months (Table 1). In July 2016 (aged 2 years), his LDL-C levels were 971 mg/dL (25.1 mmol/L) against a year-long background of similar values, and xanthomas were noted. The patient had no evidence of CV abnormalities. Standard LLT (first escalating doses of simvastatin 10 mg and 20 mg, and later rosuvastatin 5 mg/day) did not control LDL-C levels.

In November 2016, the decision was taken to conduct an orthotopic liver transplantation from an unrelated, living donor. Lipid-lowering medication was stopped. Immunosuppressive drugs were commenced (escalating doses of tacrolimus to 1.4 mg twice daily and decreasing doses of orally administered prednisolone to 2.5 mg TIW). LDL-C levels reduced to 104 mg/dL (2.7 mmol/L; Table 2).

In March 2017, the patient was briefly hospitalized for elevated LFTs due to graft rejection, in a period where alanine transaminase (ALT) and aspartate aminotransferase (AST) exceeded three times upper limit of normal at a maximum of 245 IU/L and 197 IU/L, respectively. This was treated with pulsed methylprednisolone. LDL-C levels in 2019 (3 years post-transplant and at 5 years of age) were 93 mg/dL (2.4 mmol/L) and below the target levels for a child with HoFH (Table 2). No further LFT excursions have been observed and no ASCVD has been identified.

DISCUSSION

The cases described in this series, with up to 28 years of follow-up (mean 11.7 ± 11.7 years) underscore some of the limitations of liver transplant as a broadly applicable treatment for HoFH. In these cases, liver transplant was not universally successful. Two of the Spanish patients died from surgical complications at the time of the operation under surgical practices prevalent in the 1980s. In a further Spanish patient, complications took some years to fully manifest, but ultimately resulted in death. In the second of the two Saudi Arabian cases and the Dutch case, we may be seeing emergent graft rejection given that LDL-C levels are rising, and AST and ALT levels are also on the increase.

In the remaining cases (two from Spain, one from the Netherlands, two from Saudi Arabia, and one from Turkey), only two patients (33%) were able to achieve sustained LDL-C levels in the EAS-mandated target range [1]. One of the Spanish cases required two consecutive transplants to achieve a working graft, and this liver has now failed, and the patient is facing a third transplant operation. The Turkish patient now

has LDL-C levels greater than those prior to transplantation and various options for pharmacotherapy are being considered. All but one of the patients were children or adolescents at the time of transplant, and all require chronic immunosuppressive therapy to prevent graft rejection. Most of the patients remain on LLTs.

Mortality is an established risk associated with liver transplantation in any population. Modern transplant techniques are associated with 1-, 5-, and 10-year mortality of 15%, 32%, and 50%, respectively [21]. In patients with HoFH, risks and consequences of liver transplant have been previously published. The first patient to undergo liver transplantation for HoFH was reported in 1984 [22]. The transplant, which was a combined, cardiohepatic procedure, was initially successful, and the patient's cholesterol level reduced by 75%; however, LDL-C levels stabilized at a level more than twice the recommended < 135 mg/dL (3.5 mmol/L) target for pediatric patients and the patient died 3 years after the transplant [17, 22]. In a subsequent analysis of 44 cases by Ishigaki and colleagues, while one of the patients was reported as having died at the time of the report, the authors considered the totality of the evidence to be an overall indication of successful outcomes. However, the median length of follow-up was just 1 year (range 0–10 years) [17], which may be insufficient time to reveal either the long-term mortality rate or the risk of graft rejection. In Iran, a cohort of 36 FH cases with liver transplants (80% HoFH; 70% were younger than 18 years old) and mean follow-up 24 ± 6 months revealed a mortality rate of 8% [23]. Again, this 1-year follow-up would be insufficient to determine the long-term mortality risks of liver transplantations. In the case series reported here, we determined a 30% mortality rate over a mean 11.7 years. Importantly, as patients become older, risks associated with graft revision are higher than in younger patients [24]. Therefore, should grafts made in childhood fail later in life, the consequences of graft revision should be taken very seriously.

Aside from the risks associated with major surgeries such as liver transplantation, the impact of transplant procedures on LDL-C levels in patients with HoFH is questionable. In two transplanted siblings treated directly by Ishigaki et al., neither patient achieved LDL-C targets despite use of statins and ezetimibe [17]. In the Iranian cohort of 36 mixed heterozygous FH and HoFH cases, LDL-C levels were rising at 1 year in 62% of cases. This occurred in spite of the introduction of atorvastatin 3–4 weeks after transplantation [23]. A recent case report from Slovenia described a 16-year-old patient with HoFH who underwent a deceased donor liver transplant with LDL-C levels up to 449 mg/dL (11.6 mmol/L) on LA and atorvastatin [25]. The response to liver transplant (LDL-C reduced to 201 mg/dL) (5.2 mmol/L) prompted the medical team to stop the statin and LA; however, the patient had to undergo a course of steroids for an episode of acute rejection. LDL-C levels never reached recommended targets for patients with HoFH and remained at more than double that level (approx. 160–200 mg/dL; 4.1–5.2 mmol/L), with the LDL-C levels continuously increasing at the time of the report (14.5 months post-transplant) [25]. In the case series presented here, only two of the surviving patients were able to achieve EAS guideline targets for LDL-C in patients with HoFH, and only one of these did so without additional support from standard LLTs.

The are several reasons why liver transplantation might fail to reduce LDL-C levels to normal in patients with HoFH. Transplantation attempts to replace the defective hepatic LDL-receptors with functional (wild-type) variants in the hope of restoring near-normal LDL metabolism [17]. However, only 75% of LDL-R reside in the liver [26], and transplantation does not address the issue of extrahepatic LDL-R present in other cells throughout the body. The situation is compounded by the presence of intermediate-density lipoproteins, which are also removed from circulation by LDL-R. In HoFH, these lipids remain in circulation where they are converted to LDL-C. Where residual LDL-R are present, these lipids further contribute to the overall cholesterol-driven risk of ASCVD [27]. This is supported by data from liver transplant recipients with pre-existing coronary artery disease, whereby the transplant procedure did not appear to alter the overall natural history of cardiac conditions [28]. Additionally,

heterozygous FH is the most common inherited cardiovascular disease, with the prevalence approximately 1:200–250 [29]; and 1:112 in the Gulf region [30]. These prevalences are high and therefore the chances of a matched donor having a defective LDL-R cannot be ruled out. In general, the most suitable donors for allogenic transplantation are very often relatives and there have been reports of transmission of FH via a liver graft [31]. For patients with HoFH, the chances of a relative having a defective gene for LDL-R are naturally higher than for the general population.

Should the pre-transplant genetic testing determine that no genetic abnormalities of concern are present, solid organ transplant, including liver transplant, has been associated with dyslipidemia [32]. Dyslipidemia has been reported in 31–51% of liver transplant recipients, and recommendations suggest the use of statins and other LLTs to manage this [32]. There is evidence that mechanisms of post-transplant dyslipidemia include immunosuppressant therapy, corticosteroid-induced insulin resistance and downregulation of LDL-R, and overproduction of and impaired clearance of very low-density lipoprotein cholesterol (VLDL-C) [32–34]. Additionally, surgical denervation of the graft, which is a characteristic of transplant, has been associated with derangement of lipid metabolism in graft recipients [35, 36]. Therefore, it is not surprising that reports suggest that liver transplantation elevates serum lipid markers of atherosclerosis [37].

Alongside risks of CV progression due to extended exposure to elevated levels of LDL-C, aortic stenosis can be problematic in transplant patients, even in the absence of lipid abnormalities, and there are case reports of rapid atherosclerotic progression after liver transplant [38, 39]. In patients such as these, it may be possible to control LDL-C levels after a successful procedure, but even in patients that do not have HoFH, the rate of CV events in transplanted patients ranges between 9% at 5 years and 25% at 10 years post-procedure. These rates are much higher than in age- and sex-matched controls from the general population [40]. This underscores the CV risks inherent in transplantation procedures.

Patients who have undergone a liver transplant require immunosuppressive drugs to lower the risk of graft rejection. One of the most successful modern therapies for controlling graft rejection is calcineurin inhibitors (CNIs), and they remain popular despite evidence of long-term CV risk [41]. The problem for patients with HoFH is that use of CNIs is a risk factor for hyperlipidemia. Cyclosporin, for instance, inhibits sterol 26-hydroxylase (CYP27A1), which results in reduced synthesis of hepatic bile acid, and thereby reduced transport of cholesterol from the liver [32]. In patients without HoFH requiring transplant, cyclosporin has been shown to increase LDL-C by 12–57% [32]. CNIs are metabolized via the same pathway (CYP3A4) as the high-dose statins that characterize the drug regimen for transplanted patients with HoFH [42]. Moreover, steroids, which form a mainstay of immunosuppressive therapy for transplanted patients, upregulate the synthesis of fatty acids. In turn, this results in insulin resistance and elevated hepatic VLDL synthesis. Hyperinsulinemia compounds the problem by further stimulating VLDL-C synthesis, and downregulating expression of LDL-R. All of these factors can contribute to elevated LDL-C in the context of generalized hyperlipidemia [19, 43, 44].

The effects of multiple immunosuppressive drugs on dyslipidemia may be additive [32]. Cyclosporin alone has been associated with 18% increases in circulating total cholesterol, and prednisolone with 27% increases; but add the two agents together, an increase of 44% has been observed [45]. Recommendations for the management of patients who have undergone solid organ transplantation include the use of statins and other lipid-lowering agents [32]. Post-transplant polypharmacy raises the possibility of drug–drug interactions, which have been characterized for a range of lipid-lowering agents, and include interactions with immunosuppressives [32, 46].

In the modern era of treatment of HoFH, liver transplant can be considered as an expensive last resort. Unlike other fatal disease that require a transplant, there are other effective options for treating patients with HoFH [1, 47], most of which are approved globally to treat

HoFH and have extensive long-term efficacy, safety, and real-world evidence to support their use in HoFH. These options include the microsomal triglyceride transfer protein inhibitor lomitapide, inhibitors of PCSK9 [48], inclirisan RNA therapy [49], and LA [1]. The antisense oligonucleotide mipomersen has been studied [6], but is not available in Europe. These therapies have been shown to reduce LDL-C levels in patients with HoFH, with some variations according to genotype. Lomitapide is available for the treatment of adult patients with HoFH as an adjunct to standard LLTs, including LA. Lomitapide works independently of the LDL-R pathway, and consequently has efficacy in patients with no residual LDL-R functionality [50]. Lomitapide has been shown to reduce LDL-C levels by a mean of 50% in patients with HoFH [5]. PCSK9 inhibitors operate on the LDL-R pathway to increase the cell-surface expression of LDL-R, and can reduce LDL-C levels by 20–30% [48, 51]; these agents are not effective in patients with HoFH if the LDL-R completely lacks function [48].

There are further new treatments that remain in development. These include an anti-human ANGPTL-3 antibody that has demonstrated 47% reductions in LDL-C levels in a phase 3 trial in patients with HoFH [52]. Inclisiran, a chemically synthesized small interfering RNA, has been recently approved for cholesterol lowering, and has been evaluated in a phase 2 study in HoFH where LDL-C reductions of approximately 30% were observed [49].

Gene therapies for HoFH are under development and may offer new alternatives in the treatment of HoFH [53].

Given the urgency of treatment in HoFH, these other options, such as pharmacotherapy and LA, ought to be considered first-line therapy. Progressive algorithms for treatment of HoFH support the principle that transplant is a last resort [1, 47, 54, 55].

This analysis of liver transplant in HoFH cases collected over more than 20 years in four different countries has some limitations. Principally, there is a low number of patients for formal analysis—which is a consistent feature in reports where the treatment modality under discussion is relatively uncommon within a disease that is already rare; however, the cases reported here feature wide geographical spread, including the Middle East. Some of the cases (particularly those from Spain) feature transplant protocols that have been superseded over time; it is not unreasonable to speculate that modern transplant procedures are less problematic than in the 1980s. LDL-C targets have been updated over the same period. Additionally, there are wide variations in the time elapsed from diagnosis to transplant (1–14 years), possibly driven by different levels of transplant urgency according to recipient age, the priority given to patients with HoFH, and regional variations in management of transplant waiting lists, etc. Within the individual lipid centers, not every transplanted HoFH case was captured for the purposes of this report, and origins and mutation status of the grafts are not known in all cases.

CONCLUSIONS

The cases described call into question the use of liver transplants as a primary intervention in treating HoFH and highlight the inherent mortality risk and complications associated which sometimes are only apparent years after the procedure. The ability of liver transplant to achieve LDL-C target levels is not conclusive; patients still require sometimes aggressive LLTs, with the added complexities and risks associated with transplantations such as graft versus host disease. In line with current guidelines for the treatment of HoFH [1], care teams should consider other treatment modalities before resorting to liver transplant.

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Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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