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STATE-OF-THE-ART REVIEW

Treatment of Homozygous Familial Hypercholesterolemia

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ABSTRACT

Homozygous familial hypercholesterolemia is a rare, life-threatening, genetic disorder characterized by severe hypercholesterolemia, xanthomata, and accelerated atherosclerosis. Untreated, it results in aortic root and coronary artery disease in childhood or adolescence. The introduction of plasma exchange 50 years ago marked a novel therapeutic approach to reducing low-density lipoprotein in these patients and eventually resulted in resolution of tendon xanthomas, arrested progression of atherosclerosis, and increased longevity. Here the authors describe the transition from unselective plasma exchange to the various forms of selective lipoprotein apheresis now in use and consider the remarkable developments in lipid-lowering pharmacotherapy in the current poststatin era. These include small molecules inhibiting microsomal triglyceride transfer protein, monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 and angiopoietin-like-3, and gene-directed therapies such as short interfering RNA. Finally, clustered regularly interspaced short palindromic repeats-mediated gene editing holds great promise as a one-off treatment, with the potential to permanently lower low-density lipoprotein cholesterol in both heterozygous and homozygous patients with familial hypercholesterolemia. (JACC Adv. 2025;4:101708) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In 1975, one of the authors (G.R.T.) and his colleagues published an article describing 2 patients with homozygous familial hypercholesterolemia (HoFH) who had been treated with plasma exchange for the previous 6 months.[1] This potentially fatal disorder is characterized by severe hypercholesterolemia due to mutations that impair the ability of low-density lipoprotein (LDL) receptors to bind and degrade LDL[2] and was refractory to all forms of lipid-lowering drug therapy available at the time. Repetitive plasma exchange at 3 weekly intervals, however, decreased serum cholesterol levels by approximately 50% in these FH homozygotes.

Now, 50 years later, lipoprotein apheresis, the successor of plasma exchange, remains a necessary form of treatment for some HoFH patients, as recently affirmed by the European Atherosclerosis Society (EAS)[3] and by the American Heart Association.[4] This applies not only to those with null mutations of the LDL receptor (receptor negative) but also to those with receptor defective mutations in whom combination drug therapy has variable effects and often fails to lower LDL-cholesterol (LDL-C) to guideline levels. This review describes the transition from unselective plasma exchange to the various forms of selective lipoprotein apheresis now in use

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ABBREVIATIONS AND ACRONYMS

ANGPTL3 = angiopoietin-like-3

CRISPr = clustered regularly interspaced short palindromic repeats

CVD = cardiovascular disease

EAS = European Atherosclerosis Society

FH = familial hypercholesterolemia

HoFH = homozygous familial hypercholesterolemia

LDL = low-density lipoprotein

LDL-C = low-density lipoprotein-cholesterol

Lp(a) = lipoprotein (a)

MACE = major adverse cardiovascular events

PCSK9 = proprotein convertase subtilisin/kexin type 9

and considers current and future developments in lipid-lowering drug therapy in the poststatin era (Central Illustration).

HISTORICAL BACKGROUND

The phenotypic features and pattern of inheritance of HoFH were first described by Khachadurian in Arab families in Lebanon in 1964.[5] In that same year, the first attempt to lower serum cholesterol in a child with HoFH using manual plasmapheresis was undertaken in London by Myant and Lewis but soon abandoned.[6] The following year, De Gennes et al[7] repeatedly performed manual plasmapheresis in an adult with HoFH in Paris. Although this reduced the patient's serum cholesterol by 40%, it was too demanding and was discontinued after 4 months. Both patients subsequently died from atherosclerotic cardiovascular disease (CVD) at the ages of 10 and 23, respectively.

PLASMA EXCHANGE. As stated above, one of the authors (G.R.T.) and his colleagues introduced the technique of plasma exchange to lower cholesterol levels in HoFH.[1] This was made possible by the invention of the continuous flow blood cell separator in the United States, which enabled large volumes of plasma to be exchanged at high flow rates, initially using fresh frozen plasma and subsequently heat-treated human plasma protein fraction as replacement fluids. Performed every 2 weeks for 8.4 years, this led to a 37% reduction in the mean preprocedure (maximum) level of plasma total cholesterol of 5 homozygotes, 2 treated in the United States and 3 in the United Kingdom, and resulted in a significant increase of 5.5 years in longevity compared with their untreated, deceased homozygous siblings.[8] Change in total cholesterol, 90% of which is LDL in FH homozygotes, is a preferable criterion of efficacy than change in LDL-C in patients undergoing apheresis because of the errors introduced when estimating low levels of LDL-C using the Friedwald equation.[9]

LIPOPROTEIN APHERESIS. From 1981 onward, plasma exchange was gradually replaced by lipoprotein apheresis, which initially involved selective removal of LDL by online perfusion of plasma through an immunosorbent column.[10] Immunoadsorption was soon superseded by procedures involving perfusion of plasma[11] or more recently whole blood,[12] through affinity columns containing either dextran sulfate covalently linked to cellulose beads or polyacrylate-coated polyacrylamide beads, which adsorb the apolipoprotein B component of LDL and lipoprotein (a) [Lp(a)]. Other methods include double filtration plasmapheresis, where plasma is separated from blood cells by a first filter and then perfused through a second filter which selectively retains high-density lipoprotein and albumin but discards LDL and Lp(a),[13] and the on-line precipitation of LDL by the addition of heparin to plasma, the so-called heparin-induced extracorporeal LDL/fibrinogen precipitation system.[14]

HIGHLIGHTS

- HoFH is a fatal disorder of LDL-C metabolism.
- Apheresis plus statins, ezetimibe, and PCSK9 inhibitors are currently the main forms of nonsurgical treatment.
- Lomitapide and evinacumab are very effective at lowering LDL-C, independent of LDL receptor function.
- Gene editing using CRISPr has the potential to revolutionize future management of HoFH.

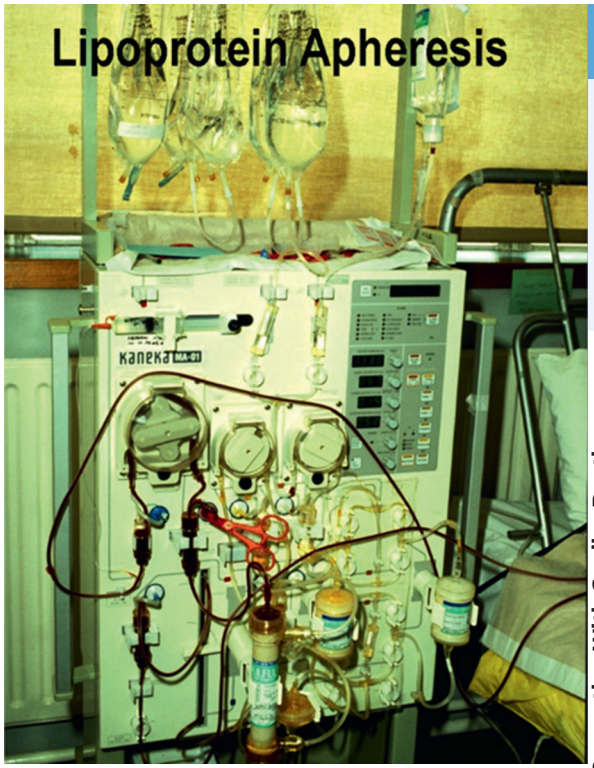
EFFICACY OF LIPOPROTEIN APHERESIS

These various methods of lipoprotein apheresis differ little in their intrinsic efficiency of LDL removal.[15] The main determinants of efficacy are the volume of blood or plasma treated and its frequency. In adults with HoFH, the aim should be to treat one to 2 plasma or blood volumes each procedure. In view of the data that the rebound in LDL is faster in receptor-negative than in receptor-defective patients, it is vital that the former undergo apheresis on a weekly basis.[16] This should theoretically achieve a 45% decrease in the interval mean vs the off-apheresis level of LDL-C, which can be decreased further by adjuvant drug therapy.[17] The interval mean (time averaged) LDL is approximately 30% lower than the preprocedure (maximum) value reached after the curvilinear rebound in LDL postapheresis, as illustrated in Figure 1, and can be calculated using the Kroon formula, as described elsewhere.[18]

GUIDELINES AND TARGETS FOR LIPOPROTEIN APHERESIS

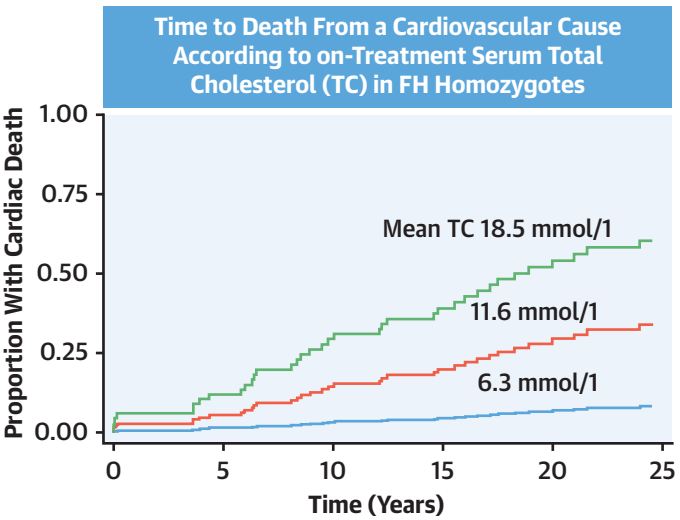
Guidelines on the use of lipoprotein apheresis to treat FH have been published in the United States,[19]

CENTRAL ILLUSTRATION **Evolution of Treatments for Homozygous Familial Hypercholesterolaemia**



Lipid-Lowering Drugs Currently Used to Treat Homozygous FH

Atorvastatin	HMG CoA reductase inhibitor
Rosuvastatin	HMG CoA reductase inhibitor
Ezetimibe	NPC1L1 inhibitor
Evolocumab	Monoclonal antibody to PCSK9
Alirocumab	Monoclonal antibody to PCSK9
Inclisiran	siRNA to PCSK9
Lomitapide	MTP inhibitor
Evinacumab	Monoclonal antibody to ANGPTL3



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Dextran sulfate adsorption lipoprotein apheresis apparatus, currently available lipid-lowering (L-L) drugs, and cardiovascular mortality in hofh according to serum cholesterol while on L-L drugs ± apheresis during 25 years of follow-up.[32] HoFH = homozygous familial hypercholesterolemia; SiRNA = small interfering RNA; other abbreviations as in Figure 2.

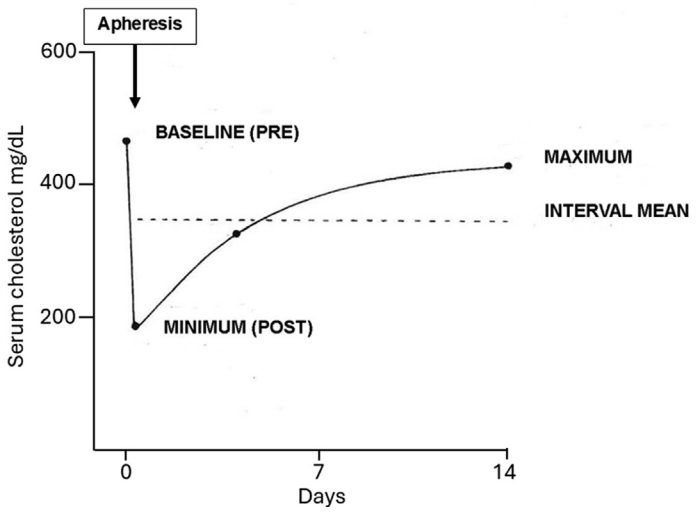
Italy,[20] Japan,[21] the United Kingdom,[22] and many other countries. In 2008, the HEART UK - The Cholesterol Charity guidelines for homozygotes advocated weekly or biweekly apheresis to achieve an interval mean total cholesterol of <270 mg/dL or LDL-C <250 mg/dL, or decreases of >60% or 65%, respectively, from levels off all treatment.[22]

Data published subsequently on CVD in French[23] and U.S.[24,25] homozygotes undergoing long-term apheresis cast doubt on the UK recommendations. In those studies, interval mean values of LDL-C were 255 and 250 mg/dL, respectively, reflecting a 64% to 69% reduction from LDL levels off treatment, but 20% to 35% of patients developed new aortic or coronary lesions or showed progression of pre-existing ones while on apheresis. Furthermore, the same outcome occurred in a Norwegian study that achieved an even lower interval mean LDL-C of 163 mg/dL by weekly apheresis plus statin/ezetimibe therapy.[26]

These findings led to the adoption by the EAS,[27] HEART UK - The Cholesterol Charity,[28] and the International Atherosclerosis Society[29] of more stringent targets for treating HoFH, namely lowering LDL-C to <135 mg/dL in children and to <100 mg/dL in adults, or to <70 mg/dL in adults with CVD. However, these levels can seldom be achieved in homozygotes by combining apheresis with conventional lipid-lowering drug therapy.

Lipoprotein apheresis acutely reduces Lp(a) to a similar extent as LDL but, unlike the latter, interval mean Lp(a) levels are uninfluenced by adjunctive therapy with statins. Observational data indicate that

FIGURE 1 Parameters of Lipoprotein Apheresis



regular apheresis leads to very low incidence rates of cardiovascular events in patients with high LDL-C and/or high Lp(a) levels, progressive CVD, and on maximally tolerated lipid-lowering medication.[30] Raised levels of Lp(a) are common in FH, but in contrast to heterozygotes,[31] have not been shown to be a risk factor for CVD in homozygotes.[32,33] However, it is possible that a persistently raised Lp(a) could become a significant residual risk factor in homozygotes not on apheresis but treated with novel drugs such as lomitapide that lower LDL but not Lp(a).[34]

SEARCH STRATEGY AND SELECTION CRITERIA

Sources of information for the manuscript included review articles and guidelines by international scientific organizations, supplemented by searches of PubMed for peer-reviewed, full-length original research articles in all languages with no restrictions based on publication date. Search terms were combinations of the following terms: "homozygous familial hypercholesterolemia," "familial hypercholesterolemia; and "lipoprotein apheresis," "apheresis," "plasmapheresis," "plasma exchange," "pharmacotherapy," "lipid lowering," "PCSK9 inhibitor," "lomitapide," "evinacumab," and "gene-editing."

LDL RECEPTOR-DEPENDENT PHARMACOTHERAPIES

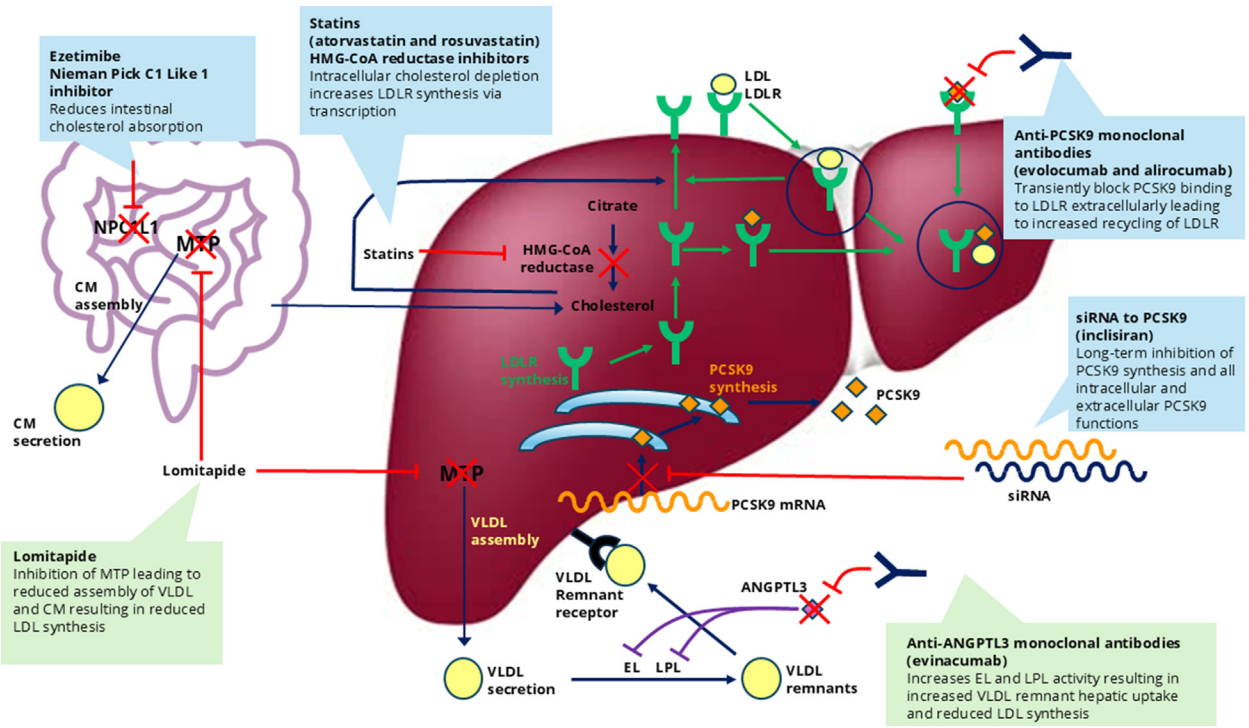
In 1973, the discovery of compactin by Akira Endo sparked a revolution in the treatment of hypercholesterolemia.[35] By inhibiting hydroxymethylglutaryl coenzyme A reductase and depleting hepatocyte cholesterol, statins cause upregulation of LDL receptors in normal subjects and in FH heterozygotes. This results in enhanced removal of LDL from plasma and a reduction in the level of LDL-C. The severity of the LDL receptor mutation determines the LDL-lowering impact of statins in FH heterozygotes, with reductions of up to 60% in those with mild mutations.

The response to statins in HoFH is widely variable, with an average reduction in LDL-C of 25% and a trend for those who are receptor defective to respond better than those who are receptor negative.[36] It is generally assumed that this reflects a less marked increase in receptor-mediated LDL catabolism in those who are receptor negative. However, studies of apolipoprotein B turnover in homozygotes undergoing apheresis showed that atorvastatin 80 mg daily decreased cholesterol synthesis and LDL production, without increasing LDL catabolism.[37] This raises the possibility that the variable response of HoFH to statins may reflect the extent to which these drugs reduce the cholesterol-driven production of LDL[38] rather than by increasing its catabolism, as occurs in FH heterozygotes. Whatever their mechanism of action, statins being safe, cost-effective, and widely available have become first-line therapy for HoFH. High-intensity agents such as rosuvastatin or atorvastatin are advocated and a reduction in cardiovascular events in statin-treated homozygotes has been demonstrated.[39]

In combination with a statin, ezetimibe, a Niemann-Pick C1-like 1 inhibitor, is recommended as first-line therapy for patients with homozygous FH and has been shown to reduce LDL-C by a further 20% in addition to a high-intensity statin.[40]

A major advance came 10 years ago with the development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which reduce the rate of degradation of LDL receptors by PCSK9 and thereby like statins promote receptor-mediated LDL uptake by the liver.[41] They also counteract the increase in PCSK9 induced by statins.[42] Their LDL-lowering effect is equivalent to that of a high dose, potent statin and is additive to the effect of the latter.

FIGURE 2 Lipid-Lowering Drugs Currently Used to Treat Homozygous FH



Blue boxes (LDLR-dependent therapies), green boxes (LDLR-independent therapies). ANGPTL3 = angiopoietin-like-3; C = cholesterol; CM = chylomicron; LDL = low-density lipoprotein; LDLR = LDL receptor; LPL = lipoprotein lipase; EL = endothelial lipase; MTP = microsomal triglyceride transfer protein; PCSK9 = proprotein convertase subtilisin/kexin type 9; VLDL = very low-density lipoprotein; FH = familial hypercholesterolemia; HMG-CoA = hydroxymethylglutaryl coenzyme A.

Currently approved pharmacological approaches to inhibiting PCSK9 are two-fold. Humanized monoclonal antibodies (evolocumab or alirocumab) to block PCSK9 are given by subcutaneous injection every 2 to 4 weeks. Two open-label trials of evolocumab in patients with moderately raised LDL levels, including those with heterozygous FH, showed that doses of 140 mg every 2 weeks or 420 mg monthly reduced LDL-C by 61% and halved the risk of major adverse cardiovascular events (MACE).[43] Injection-site reactions were reported in 4.3% of patients and led to its discontinuation in 0.2%. However, the efficacy of evolocumab in patients with HoFH both on or not on apheresis is much less, reductions in LDL-C from baseline averaging only 23%.[44] Under similar circumstances alirocumab reduced LDL-C from baseline by 27%.[45]

The 2023 EAS consensus statement recommends that monoclonal PCSK9 inhibitors are added within 8 weeks of a diagnosis of HoFH.[3] The American Heart Association recommends that a monoclonal PCSK9 inhibitor should be added if LDL-C remains above target after 6 months of statin therapy in combination with ezetimibe.[46] However, as with the other LDL receptor-dependent therapies, the effectiveness of PCSK9 inhibitors in HoFH remains variable with 0% to 60% reductions in LDL-C reported in trials.[44,45,47] It is for this reason that the EAS recommends a trial of 1 to 2 doses of a monoclonal PCSK9 inhibitor and considering its continuation only if >15% reduction in LDL-C is achieved.[3]

More recently, inclisiran, a small interfering RNA nucleotide molecule that, when given twice yearly as a subcutaneous injection, prevents the translation of PCSK9 in the liver, has been licensed for LDL-C reduction.[48] However, in the ORION-5 trial in patients with HoFH, the placebo-corrected decrease in LDL-C was only 1.7%.[49]

TABLE 1 Effects of PE, LA + Statin ± Ezetimibe, and Lipoprotein Apheresis + Statin + Ezetimibe + or Statin + Ezetimibe + L on Serum Cholesterol and MACE in FH Homozygotes Referred to Hammersmith Hospital Since 1976

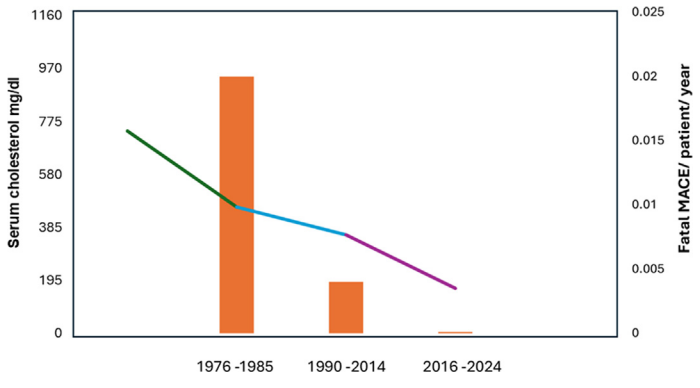
Rx[a]	n	Period	TC[b] Pre-Rx	TC[b] on Rx	Δ TC, %	MACE, n	MACE/ Patient/Year
PE	5	1976-1985	697 ± 34	457 ± 10.4[c]	−37	3[d]	0.07
LA	9	1990-2014	820 ± 209	356 ± 104[c]	−57	9[d]	0.04
LA + L	4	2016-2024	302 ± 112	162 ± 70[c]	−46	1	0.04
L	2	2022-2024	259	163	−37	0	0

[a]Treatment. [b]Total cholesterol, mg/dL (mean ± SD). [c]Preprocedure (maximum) value. [d]1 fatal.
FH = familial hypercholesterolemia; L = lomitapide; LA = lipoprotein apheresis; MACE = major adverse cardiovascular events; PE = plasma exchange.

LDL RECEPTOR-INDEPENDENT PHARMACOTHERAPIES

In patients with little or no LDL receptor function, the therapies outlined in the previous section have limited efficacy and there is still a large unmet need in LDL-lowering strategies for patients with HoFH. Across the world, such patients are undertreated, with a median LDL-C of 150 mg/dL on treatment in high-income countries and 360 mg/dL in nonhigh-income countries.[50] Recently, 2 alternative pharmacological agents that act independently of the LDL receptor have been approved to treat patients with HoFH: lomitapide and evinacumab.

FIGURE 3 Temporal Improvements in Efficacy of Cholesterol Lowering is Associated With a Reduction in Fatal Major Adverse Cardiovascular Events



Temporal improvements in efficacy of cholesterol-lowering therapy in FH homozygotes: 1976 to 1985 plasma exchange; 1990 to 2014 lipoprotein apheresis + statin ± ezetimibe; 2016 to 2024 lomitapide ± lipoprotein apheresis + statin + ezetimibe. Columns represent fatal major adverse cardiovascular events (MACE)/patient/year. Line represents serum total cholesterol (mg/dL). Abbreviation as in Figure 2.

Lomitapide, a small molecule inhibitor of the microsomal triglyceride transfer protein (MTP), binds directly to MTP in the endoplasmic reticulum of hepatocytes and enterocytes, thereby inhibiting the assembly of very LDL and chylomicrons.[51] Clinical trials have shown that lomitapide can reduce LDL-C concentrations by approximately 50%.[52] A real-world study of 75 homozygotes across 9 European countries suggests even better results with LDL-C reductions of 60% after a median duration of 19 months. Importantly, prior to lomitapide, 38 patients were receiving lipoprotein apheresis, but after initiation of lomitapide 37% of patients discontinued apheresis as they met their LDL-C target.[53] In some patients, the replacement of apheresis by a once-daily tablet of lomitapide has been life-changing.

However, treatment with lomitapide was permanently interrupted in 13% of patients, with gastrointestinal symptoms occurring in 40%. Given the action of lomitapide on chylomicron assembly, patients need to adhere to a very low fat diet (<20% of total calorie intake) which can be challenging. Steatosis within the gastrointestinal tract can otherwise lead to bloating, diarrhea, and flatulence. Also of relevance is the impact of lomitapide on hepatic fat accumulation. Analysis of aggregated data from the phase III trial, Lomitapide Observational Worldwide Evaluation Registry and an Italian cohort has shown that, overall, lomitapide has a favorable long-term hepatic safety profile and, to date, hepatic fat has only moderately increased while hepatic stiffness has remained normal over a 9-year follow-up.[54] These real-world studies have predominantly employed ultrasonography or hepatic elastography for cost and availability reasons. MRI-based techniques may provide superior diagnostic accuracy and reliability for evaluating long-term hepatic complications. Longer term safety

data are being collected in the worldwide Lomitapide Observational Worldwide Evaluation Registry registry[55] and ongoing surveillance remains important over extended periods of use (15-20 years).

More recently, evinacumab, a monoclonal antibody that inhibits angiopoietin-like-3 (ANGPTL3), has been shown to reduce LDL-C in HoFH patients by 47%.[56] In a subsequent observational study in France, evinacumab lowered LDL-C in 12 homozygotes by 56% to 108 mg/dL. None of the evinacumab-treated patients, 10 of whom were on lipoprotein apheresis, experienced a cardiovascular event over a 4-year period, compared with 24% of a control cohort matched for apheresis but not on evinacumab or lomitapide.[57]

The mechanism of action of evinacumab reflects its ability to inhibit ANGPTL3, an inhibitor of lipoprotein lipase and endothelial lipase. This promotes lipolysis and leads to the reduction of LDL in HoFH by an endothelial lipase-mediated pathway that results in LDL receptor-independent hepatic clearance of very LDL remnants prior to their conversion to LDL.[58] Administered as a monthly one-hour intravenous infusion, evinacumab may be preferable for patients who cannot tolerate lomitapide and for whom apheresis is not available. **Figure 2** summarizes the features of currently available drugs used to treat HoFH. Several small interfering RNA-based therapies targeting ANGPTL3 are also currently in development.[59]

The 2023 EAS consensus statement recommends addition of lomitapide and/or ANGPTL3-directed therapy in patients with HoFH if LDL-C targets are not met. Both lomitapide and evinacumab are very expensive and therefore may not be viable options for many health care systems. Where local expertise exists, apheresis may continue to be the most cost-effective LDL receptor-independent therapy.

CLINICAL OUTCOMES OF COMBINING APHERESIS WITH LIPID-LOWERING DRUG THERAPY: A SINGLE-CENTER EXPERIENCE

Table 1 summarizes nearly 50 years' experience of managing HoFH patients referred to Hammersmith Hospital, London.

Between 1976 and 1985, plasma exchange reduced serum cholesterol by 37% from 731 to 457 mg/dL, with a MACE rate of 0.07/patient/year, 20% of which were fatal.

Between 1990 and 2014, lipoprotein apheresis combined with a statin ± ezetimibe reduced serum cholesterol by 57%, from 820 to 356 mg/dL with a MACE rate of 0.04/patient/year, 11% of which were fatal.

Between 2016 and 2024, adding lomitapide to lipoprotein apheresis plus a statin and ezetimibe reduced serum cholesterol by 46% from 302 to 163 mg/dL, with a MACE rate of 0.04/patient/year but no fatalities. Between 2022 and 2024, 2 patients who refused apheresis were treated with a statin, ezetimibe, and lomitapide, which reduced their serum cholesterol by 37% from 259 to 163 mg/dL, without occurrence of a MACE. Combining the data from all 6 patients treated with lomitapide, the latter reduced serum cholesterol from 286 ± 97 to 163 ± 58 mg/dL ($P < 0.005$).

Although the numbers are small, these data support the use of lomitapide as an adjunct to lipoprotein apheresis in the treatment of HoFH, or in some instances an alternative. The progressive decrease in serum cholesterol and downward trend in fatal MACE with improvements in treatment between 1976 and the present day are illustrated in **Figure 3**. Comparable decreases in LDL-C were reported recently in 39 FH homozygotes in the SAFEHEART study (Spanish Familial Hypercholesterolemia Cohort Study) treated with lipid-lowering measures that included lipoprotein apheresis and lomitapide and were accompanied by reductions in MACE during 11 years of follow-up.[60]

FUTURE DEVELOPMENTS

In recent years, the development of gene silencing therapies has gained real momentum,[61] while gene therapy techniques, whereby a "faulty" gene is replaced by a "healthy" copy of the gene, are still in development (NCT02651675). More recently, exosome-based LDL receptor gene therapy has been explored. An exosome is a disk-shaped vesicle originating from the endosome of the nucleus, a "natural nanoparticle," that can be loaded with mRNA. Compared with artificial nanoparticles, exosomes have decreased immune response, enhanced bioavailability, reduced toxicity and potential for selective drug delivery. The first human study of exosome-based LDL receptor mRNA delivery began in December 2021 in a phase I clinical trial (NCT05043181), involving 30 patients diagnosed with HoFH and the results are eagerly awaited.

Finally, of great potential, is the prospect of in vivo gene editing employing clustered regularly interspaced short palindromic repeats (CRISPr)-Cas9 and-Cas12 nucleases or CRISPr base editors. CRISPrR base editors are an attractive gene-editing modality because they introduce precise targeted alterations efficiently without the need for double-strand breaks.

Verve Therapeutics are developing 2 CRISPr base-editing medications targeting PCSK9 (Verve-101 and -102) and ANGPLT3 (Verve-201), the former already being in phase one clinical trials in FH heterozygotes.[62] This could lead to permanent lowering of LDL-C after a one-off intravenous infusion of the base editor. The long-term safety of base editing needs to be evaluated and patients in the phase one trial will be monitored for 15 years. However, for patients with HoFH, in whom the benefit potentially outweighs the risk, base-editing of ANGPTL3 could be life-changing and -prolonging.

CONCLUSIONS

Despite remarkable developments in lipid-lowering drug therapy over the last 50 years, lipoprotein apheresis remains a mainstay of treatment for HoFH. Life expectancy for these patients has increased further with the advent of newer LDL receptor-independent therapies. Gene editing holds great promise as a one-off treatment, with the potential to permanently lower LDL-C in both heterozygous and homozygous FH patients.

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