The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Review

J Atheroscler Thromb, 2022; 29: 1125-1135. http://doi.org/10.5551/jat.RV17065

Advancements in the Treatment of Homozygous Familial Hypercholesterolemia

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Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder with extreme elevations of low-density lipoprotein cholesterol (LDL-C) leading to premature atherosclerotic cardiovascular disease (ASCVD) as early as in childhood. Management of HoFH centers around aggressive and adequate reduction of LDL-C levels to slow the trajectory of ASCVD development. Historically, lowering LDL-C levels in HoFH has been challenging because of both the markedly elevated LDL-C levels (often >400 mg/dL) and reduced response to treatment options, such as statins, for which the mechanism of action requires a functional LDL receptor. However, the treatment landscape for HoFH has rapidly progressed over the last decade. While statins and ezetimibe remain first-line treatment, patients often require addition of multiple therapies to achieve goal LDL-C levels. The PCSK9 inhibitors are an important recent addition to the available treatment options, along with lomitapide, bile acid sequestrants, and, possibly, bempedoic acid. Additionally, ANGPTL3 has emerged as an important therapeutic target, with evinacumab being the first available ANGPTL3 inhibitor on the market for the treatment of patients with HoFH. For patients who cannot achieve adequate LDL-C reduction, lipoprotein apheresis may be necessary, with the added benefit of reducing lipoprotein(a) levels that carries an added risk if also elevated in patients with HoFH. Finally, gene therapy and genome editing using CRISPR/Cas-9 are moving through clinical development and may dramatically alter the future landscape of treatment for HoFH.

Key words: **Familial hypercholesterolemia, PCSK9, ANGPTL3, Apheresis, Gene therapy**

Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder with extreme elevations in low-density lipoprotein cholesterol (LDL-C) leading to premature atherosclerotic cardiovascular disease (ASCVD)[1, 2]. Based on the frequency of heterozygous FH (HeFH) found in two recent meta-analyses[3, 4], HoFH is estimated to have a prevalence of 1:300, 000–1:360, 000[1, 3-5] but may be more common in isolated or founder populations[1]. The disorder is caused by mutations in genes regulating activity of the LDL receptor (LDLR). Most patients with HoFH have biallelic loss-of-function (LOF) mutations in the *LDLR* gene, which encodes for the LDLR itself. Biallelic mutations may be either two identical copies of the same allele (simple homozygote) or two nonidentical alleles (compound heterozygote). Patients with genetically confirmed HoFH have also been found to have biallelic mutations in *APOB*, which encodes apolipoprotein B (apoB); *PCSK9*, which encodes the pro-protein convertase subtilisin/kexin type 9 (PCSK9) enzyme; or *LDLRAP1*, which encodes the LDLR adapter protein 1 [1]. Rarely, genetically confirmed HoFH has been found to have one heterozygous mutation in *LDLR* together with a heterozygous mutation in either *APOB* or *PCSK9* (double heterozygote)[1]. By altering LDLR activity and reducing LDL-C uptake from circulation, these genetic changes result in a marked increase in circulating LDL-C level starting at birth. After ruling out secondary factors that may influence hypercholesterolemia, an LDL-C level >400 mg/dL (>10 mmol/L), together with a positive family history

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Received: March 1, 2022 Accepted for publication: March 18, 2022

of hypercholesterolemia and/or early presence of xanthomas, is suggestive of HoFH[5, 6].

Patients with HoFH develop early and progressive ASCVD and may experience events such as myocardial infarctions as early as in childhood[1, 7]. The high mortality and morbidity result from the lifelong exposure to the high cholesterol burden associated with the disease[8, 9]. Thus, early diagnosis and initiation of lipid-lowering treatment are paramount to reduce the clinical severity associated with this disorder[10]. Management of HoFH centers around aggressive and adequate reduction of the circulating LDL-C level to slow the trajectory of atherosclerotic disease development[11, 12]. The importance of this approach is demonstrated by the results from the HoFH International Clinical Collaborators registry, which clearly show how greater use of multiple lipid-lowering treatment regimens is associated with lower LDL-C levels and better outcomes in patients worldwide[7]. Historically, lowering LDL-C levels in HoFH has been challenging, because of both the markedly elevated levels and reduced response to treatment options, such as statins, whose mechanism of action requires a functional LDLR. However, the treatment landscape has rapidly progressed in the last decade with the development of several novel therapeutics that have transformed HoFH into a manageable condition.

Current Treatment Approaches for HoFH

The treatment algorithm in HoFH is similar to what is used for other conditions in which LDL-C reduction is required for ASCVD risk reduction, and the treatment goals are the same. However, what differentiates the approach in HoFH is that treatment must start at the time of diagnosis, which could be in early childhood, and often necessitates an aggressive strategy requiring multiple therapeutics, pharmacological and not, given the difficulty in lowering LDL-C in this condition[1, 2].

Pharmacological Interventions - LDLR-Dependent Mechanisms

Statins, Ezetimibe, and Bile Acid Sequestrants

High-intensity statins (HMG-CoA reductase inhibitors) and ezetimibe are available worldwide and are considered a first-line treatment that should be started at the time of diagnosis. The LDL-C-lowering effect of statins varies and depends on the residual LDLR activity present; however, some lipid-lowering effect is also seen in LDLR-negative patients, possibly because of an effect on cholesterol synthesis and/or apoB-containing lipoprotein production, which are both increased in these patients[13, 14]. Ezetimibe, an inhibitor of the Niemann-Pick C1-Like 1 (NPC1L1) protein, inhibits cholesterol absorption and adds an additional 10%–15% reduction in LDL-C levels[15, 16] and should be added to statin therapy as a second LDL-C-lowering agent. Statins, alone and in combination with ezetimibe, have been shown to reduce CVD mortality in patients with HoFH[17], including in the pediatric population[10]. Bile acid sequestrants also provide a modest reduction in LDL-C levels up to 15% when added to statin therapy in patients more broadly than HoFH[18], and are another option for add-on LDL-C-lowering therapy for these patients. However, these treatments are rarely, if ever, sufficient to achieve adequate LDL-C reduction, and additional lipid-lowering treatments are necessary.

PCSK9 Inhibitors

PCSK9 is a key protein in the posttranslational regulation of the LDLR[19]. The discovery that carriers of LOF variants in the *PCSK9* gene have low LDL-C levels and a significant reduction in the risk of developing ASCVD[20, 21] brought to light the prospect of PCSK9 as a promising drug target. The PCSK9 inhibitor monoclonal antibodies, evolocumab and alirocumab, are relatively recent additions to the LDL-C-lowering category of therapies. In clinical trials, evolocumab was shown to reduce LDL-C by 31% at 12 weeks in 49 patients with HoFH on stable background lipid-lowering therapy that did not include apheresis[22]. In a long-term outcomes study published recently, open-label evolocumab at a dose of 420 mg administered once monthly or every 2 weeks if on lipoprotein apheresis resulted in an approximately 24% additional reduction in LDL-C levels in over 100 patients with HoFH, approximately 30% of whom were also receiving apheresis[23]. More recently, in a placebo-controlled randomized trial of 69 patients with HoFH, alirocumab at a dose of 150 mg administered every 2 weeks was shown to reduce LDL-C levels by approximately 35% at 12 weeks[24].

PCSK9 inhibition has been also successfully achieved using a small interfering ribonucleic acid (siRNA). Inclisiran is an siRNA for PCSK9 that has been approved in Europe and was recently approved by the United States Food and Drug Administration (FDA). The siRNA molecules bind to the mRNA of the *PCSK9* gene to limit translation and synthesis of the protein. In pooled analysis of multiple phase 3 clinical trials of inclisiran in patients with ASCVD or HeFH, inclisiran was associated with approximately 50% reduction in LDL-C levels at day 510 [25]. As compared with mAb preparations that require monthly or every 2-week dosing, inclisiran has the

advantage of requiring very infrequent dosing for the patient. After an initial 300-mg dose delivered as a subcutaneous injection, the next dose is at 3 months followed by dosing every 6 months thereafter, offering the convenience of administration at routine clinical visits in the physician's office. Similar to evolocumab and alirocumab, the response to inclisiran in patients with HoFH is lower than that in those with HeFH and is variable. In a pilot study of four patients with HoFH, inclisiran was associated with an LDL-C reduction ranging from 17.5% to 37.0% at day 180 in three out of the four patients and not responsive in the fourth patient[26]. A long-term phase 3 trial of inclisiran in patients with HoFH (ORION-5; NCT03851705) is currently ongoing.

The safety and tolerability profile of the PCSK9 inhibitors are strong and favorable. The most common side effect is injection site reaction for both the siRNA and mAb drugs. However, given the costs that these medications carry, it is reasonable to consider stopping their use in unresponsive patients and starting another lipid-lowering approach.

In keeping with their mechanism of action, response to PCSK9 inhibitors depends in part on the residual LDLR activity[23] even among individuals with identical *LDLR* mutations[27]. Consequently, in patients that have no or minimal LDLR activity, and in patients with untreated LDL-C levels that are exceedingly high, additional lipid-lowering treatment is needed, especially those that are able to reduce LDL-C in a receptor-independent manner, such as lomitapide, ANGPTL3 inhibitors, or lipoprotein apheresis.

Pharmacological Interventions – LDLR-Independent Mechanisms

Lomitapide

Lomitapide is a small molecule specifically approved for the treatment of HoFH[28]. It offers substantial LDL-C reduction by inhibiting the microsomal triglyceride transfer protein (MTTP) to reduce production of very low-density lipoprotein (VLDL) and LDL independently of LDLR residual activity[29]. In a phase 3 clinical trial in 29 patients with HoFH, lomitapide at a median dose of 40 mg daily was shown to reduce LDL-C by 50% in the first 26 weeks and by 38% at week 56 [30]. A phase 3 extension study in a cohort of eight Japanese patients with HoFH confirmed LDL-C reductions of approximately 50% with lomitapide in this population at >60 weeks with no additional safety concerns[31]. Despite the impressive lipid-lowering effect, the use of lomitapide has been limited because of the expected adverse effects linked to its mechanism of action. The commonly reported side effects and reasons for discontinuation include increases in liver fat, transaminase levels, patient tolerability, and gastrointestinal side effects, such as nausea and diarrhea[28]. Despite an increase in hepatic fat, long-term follow-up assessing safety up to a median 5.1 years in patients that participated in the phase 3 study did not show any new safety concerns[32]. Further, recent real-world data suggests that a strategy of appropriate diet modification with dose titration personalized to the patient with dose reductions as needed to offset safety and tolerability issues, and likely improving compliance, allows for significant LDL-C reductions. In a study based out of Italy, 15 patients with HoFH experienced a mean 68.2% reduction in LDL-C levels with the addition of lomitapide to background lipid-lowering therapy at an average dose of only 19 mg/day[33]. In a more recent study that is in line with these findings, 12 patients with HoFH on lipid-lowering therapy (with or without apheresis) showed that the addition of lomitapide was associated with a greater than 50% reduction in LDL-C levels at an average dose of about 20 mg/day[34]. Lomitapide has also been shown to have good safety, tolerability, and effectiveness in the pediatric population, with a recent study describing its use in patients as young as 4 years old[35]. A clinical trial of lomitapide in the pediatric HoFH population is currently recruiting (NCT04681170).

ANGPTL3 Inhibitors

The angiopoietin-like 3 (ANGPTL3) protein emerged to the forefront as an attractive target for LDL-C reduction only a few years ago, after subjects carrying LOF mutations in the gene encoding for ANGPTL3 were noted to have low levels of several lipid parameters, including LDL-C[36]. Subsequent large-scale genetic studies have shown that LOF variants in the *ANGPTL3* gene are also associated with reduced risk of cardiovascular disease[37, 38]. Since then, ANGPTL3 inhibitors have been developed for both hypertriglyceridemia and FH. Evinacumab, a monoclonal antibody that inhibits ANGPTL3, was recently approved in Europe and the United States for patients with HoFH. In a placebo-controlled phase 3 trial of 65 patients with HoFH, evinacumab, given as an infusion at a dose of 15 mg/kg of body weight once every 4 weeks, was associated with a 47% LDL-C reduction at week 24, and the reduction was similar in patients with and without *LDLR* null variants, supporting an LDLR-independent mechanism[39].

Although the mechanism by which inhibiting ANGPTL3 lowers LDL-C remains unclear, animal models[40, 41] and a recent kinetics study in patients

with HoFH treated with evinacumab[42] suggest that the effect of ANGPTL3 inhibitions in reducing LDL-C levels is primarily driven by an increase in clearance of remnant particles and LDL from the circulation.

With a favorable safety profile, reported good tolerability, and a remarkable LDL-C-lowering response, this new addition to the armamentarium of approved lipid-lowering treatments may have the potential to significantly alter the treatment approach for HoFH.

In addition to the use of mAB, RNA-targeted approaches to inhibit ANGPTL3 are being tested. Results using an antisense oligonucleotide (ASO) against ANGPTL3 in patients with hypertriglyceridemia and FH have been recently published[43]. Interesting preclinical data in a mice model of HoFH (*Ldlr -/-* mice) co-treated with ASOs against *Mttp* and *Angptl3* showed a mitigation of the hepatosteatosis caused by the inhibition of Mttp[43], suggesting that co-administration of lomitapide with an RNA-targeted ANGPTL3 inhibitor may be able to reduce the hepatic lipid accumulation caused by lomitapide treatment. An siRNA, ARO-ANG3, targeting the *ANGPTL3* gene is currently being tested in a phase 1 clinical trial with 40 healthy volunteers and over 50 subjects with various dyslipidemic conditions (NCT03747224). Early results from healthy volunteers following dose-varying subcutaneous injections of ARO-ANG3 on days 1 and 29 showed a 45%–54% decrease in LDL-C at 4–6 weeks following the second dose[44]. If efficacy of this siRNA-based ANGPTL3 inhibitor is confirmed in HoFH, it is possible that dosing could be less frequent, similar to that of inclisiran.

Other Potential Additions in Drug Therapies for HoFH

Bempedoic acid, an oral medication that is an inhibitor of adenosine triphosphate citrate lyase, was recently approved in the United States and European Union[45]. It has been shown to offer an additional 15%–20% reduction in LDL-C levels in clinical trials of patients with ASCVD or heterozygous FH on maximally tolerated statins[46, 47]. The CLEAR Outcomes trial evaluating cardiovascular outcomes with bempedoic acid compared to placebo in patients with cardiovascular disease or risk factors is currently ongoing (NCT02993406)[48]. No data are yet available to see if bempedoic acid is effective in HoFH, but it is possible that patients with residual LDLR activity will respond to it.

Gemcabene, a peroxisome proliferation-activated receptor (PPAR alpha) agonist, is an oral therapy that enhances VLDL clearance and inhibits hepatic production of cholesterol. In the COBALT-1 study, gemcabene was shown to reduce LDL-C by a mean of 26% in eight patients with HoFH[49]. However, development of gemcabene was placed on partial clinical hold by the US FDA in 2016 as the FDA requested additional animal carcinogenicity studies.

Nonpharmacological Treatments

Lipoprotein Apheresis

Despite several options in LDL-C-lowering drug therapies, most patients with HoFH remain far from achieving adequate LDL-levels, and studies have shown that the survival in patients with HoFH largely depends on the extent of LDL-C reduction[11]. For a long time, lipoprotein apheresis had been the only effective way to treat HoFH, and oftentimes, it is still a necessary component of the treatment strategy in patients with HoFH. Although no randomized trials have been conducted, several retrospective studies have shown the effectiveness of lipoprotein apheresis in reducing LDL-C levels and reducing rates of cardiovascular outcomes[50]. Lipoprotein apheresis is associated with a significant acute reduction in LDL-C, upward of 50%–60%[51], and a mean 21%–36% reduction over the long term[52]. In a systematic review assessing studies of apheresis in the pediatric populations, the authors found that across 76 studies of children with HoFH, apheresis resulted in mean LDL-C reductions of approximately 60%–70% following an apheresis session and that xanthomas resolved in 83% of cases[53]. Lipoprotein apheresis offers the additional benefit of lowering lipoprotein(a) [Lp(a)][54], which is another driver of ASCVD risk in patients with both HoFH and elevated lipoprotein(a) levels.

Apheresis treatments at weekly or biweekly schedules can be burdensome and difficult to tolerate for some patients[55], and proximity to apheresis centers limits availability to a fraction of the HoFH patient population[56]. Despite some limitations, lipoprotein apheresis is one of the few effective available resources in less affluent countries and where access to novel treatment may be more difficult, but ad hoc government programs are available.

Liver Transplant

Liver transplant is considered a definitive treatment for HoFH, with dramatic LDL-C reductions of up to 80% following transplant[57]. It has been done in relatively few cases of HoFH, sometimes in combination with heart transplantation. A recent review identified 44 cases of liver transplant for HoFH following the first reported case in 1984 [57]. In a study

of eight pediatric patients with HoFH in the United States who underwent liver transplant, there were four who were followed up 4–6 years following surgery[58]. During this follow-up period, coronary artery disease did not develop in any of the four patients, except in one minor artery in one patient, and actually regressed in two patients who originally had >50% stenosis. Contrary to this, aortic valve stenosis, another important clinical sequela of HoFH, continued to progress in two of the four patients. Despite the potential resolutive treatment, the risks and complications associated with the surgery, and the necessary long-term immunosuppressant therapy, greatly limit this approach as a treatment option to very rare instances[1, 57].

Targeting Lipoprotein(a) to Reduce Residual Risk in HoFH

Through large-scale genetic studies, lipoprotein(a) has been shown to be causally associated with ASCVD and calcific aortic valve stenosis, independent of LDL-C levels[59, 60]. Lp(a) levels are largely inherited, driven by the *LPA* gene locus, and elevated levels above what is considered normal (<30 mg/dL or 75 nmol/L) are associated with disease in a continuous and linear manner[61]. Lp(a) levels have been shown to be higher in patients with HoFH than in those with heterozygous FH and those without any FH-causing mutations[62, 63]. In a study of 119 patients in the Netherlands with FH-causing mutations and unaffected family controls, median Lp(a) levels were 47.3 mg/dL in the 20 patients with HoFH compared to 24.4 mg/dL in the 50 patients with HeFH and 19.9 mg/dL in 22 unaffected family members[62]. There is currently no approved drug for Lp(a) lowering and the majority of LDL-C-lowering therapies used for patients with HoFH do not significantly affect Lp(a) levels. The PCSK9 inhibitor monoclonal antibodies offer a modest reduction in Lp(a) of about 20%–25% in patients with HoFH[24, 64]. Lipoprotein apheresis has been shown to lower Lp(a) levels by 53%–73% across all patients, not just those with HoFH, with elevated Lp(a) levels[65].

There are several novel therapeutics in various stages of clinical development that target Lp(a): two siRNA products, olpasiran (NCT04270760) and SLN360 (NCT04606602), and an ASO, pelacarsen (NCT04023552). Pelacarsen is furthest along and being studied in an ongoing phase 3 clinical trial. In the phase 2 study with 286 participants with established cardiovascular disease and Lp(a) at least 60 mg/dL at baseline, pelacarsen at a dose of 20 mg injected subcutaneously every week was associated with an 80% mean reduction in Lp(a) levels[66]. An equivalent dose of 80 mg every 4 weeks is being tested against a placebo in the phase 3 trial (NCT04023552) to evaluate whether this reduction in Lp(a) levels will be associated with a reduction in cardiovascular outcomes. If shown effective, Lp(a)-lowering therapy may offer patients with HoFH and elevated Lp(a) levels another avenue for risk reduction orthogonal to that achieved with LDL-C reduction.

Future Directions in the Treatment of HoFH

Given the fast-paced advancement in biotechnologies, several therapies using mAb, RNA-based therapeutics, and gene silencing, editing, and transfer are currently being explored for the treatment of HoFH. As mentioned above, mAbs against PCSK9 and ANGPTL3 are already an invaluable tool available for its treatment. Mipomersen, an ASO against apoB[67], is no longer in clinical use, but it was one of the first RNA-based treatments to be approved, and other ASO and/or siRNA strategies targeting PCSK9 and ANGPTL3 have already been tested in clinical trials as mentioned above[25, 26, 44]. Gene transfer and gene editing are the next frontier being explored for the treatment of HoFH.

Adeno-Associated Virus-Mediated Gene Transfer

Based on the correction of the metabolic defect and the normalization of LDL-C levels following liver transplant, liver-directed gene transfer is a therapeutic approach that has the potential to substantially improve the response to available treatment methods, if not to be completely curative. After an early attempt using an ex vivo approach[68], the discovery of the adeno-associated virus (AAV) as a vector for the delivery of the transgene has allowed great progress, as it is less immunogenic and at lower risk of integration into the host genome as compared with other viral vectors. AAV-mediated gene transfer has already proved to be a successful approach in the treatment of monogenic conditions[69, 70]. Specifically, the AAV8 serotype has demonstrated a high tropism for the liver and has shown therapeutic response in early trials in patients with hemophilia[71, 72]. Preclinical studies using AAV8-mediated gene transfer have been successful in expressing LDLR in the liver and reducing LDL-C levels and atherosclerosis in *Ldlr* KO mice, with no significant safety concerns[73-75]. A phase 1/2 first-in-human clinical trial of an AAV-mediated *hLDLR* gene transfer in nine patients with HoFH was recently completed (NCT 02651675). Although no information on efficacy is yet available, early reports from the study showed a dose-dependent elevation in liver transaminases. Transaminase elevations have also been observed in other AAV-mediated gene transfer trials[71, 76]

and have been attributed to a T-cell immune response to the vector capsid. As in previous studies, the transaminase elevation responded to steroid treatment and was effectively mitigated by the use of a prophylactic steroid regimen[77]. Results of the LDL-C response to the AAV-vector therapy in the HoFH trial are pending.

CRISPR-Based Genome Editing

CRISPR-based gene editing has made a great leap of advancement in the last decade[78], reaching early phase clinical trials and recently showing remarkable success in treating sickle cell[79] and transthyretin amyloidosis[80]. Relevant to HoFH treatment, correction of the *LDLR* genetic defect and recovering of its function have been demonstrated using iPS cells derived from a patient with HoFH[81]. Correction of the genetic defect and reduction in cholesterol levels and atherosclerotic plaques have been also demonstrated *in vivo* using a mouse model engineered to carry a known *LDLR* pathogenic variant[82]. Alternatively, CRISPR-based genome editing has also been successfully used to lower LDL-C levels by targeting *ANGPTL3* in *Ldlr* KO mice using an adenoviral vector to deliver the CRISPR base editors[83]. Interestingly, because viral vectors, such as AAVs, may have size limitation to deliver the base editor, non-viral alternatives, such as lipid nanoparticles, have also been used[84]. Researchers have successfully used CRISPR base editors delivered using lipid nanoparticles to modify *PCSK9* in mice and primates, with an observed 90% reduction of PCSK9 enzyme levels and 60% reduction in LDL-C levels in primates that remained stable at 8 months following treatment[85]. The use of lipid nanoparticles is particularly interesting, as it may be less immunogenic than a viral vector. It remains unclear if this approach is effective also in animal models lacking the LDLR. Nevertheless, these results are very promising.

Conclusions

Effective treatment and management of patients with HoFH remain a challenge for today's healthcare community, but novel additions to the available therapeutic approaches give reason for optimism. Reducing the high morbidity and mortality in HoFH is strongly linked to the success of LDL-C lowering[7, 11]. As per recommendations set forth by the European Atherosclerosis Society, target LDL-C levels are <100 mg/dL (<2.5 mmol/L) in adults with FH, <70 mg/dL (<1.8 mmol/L) in adults with FH with CVD, and <135 mg/dL (<3.5 mmol/L) in children with FH irrespective of the presence of CVD[1]. To reach these targets, patients with HoFH almost universally require multiple therapeutic approaches, often in conjunction with lipoprotein apheresis. Statins in combination with ezetimibe remain the first-line treatment in this population and need to be started at the time of diagnosis, including early childhood. As this combination alone is usually not sufficient in achieving adequate reduction in LDL-C, additional treatment options must be added to reach target LDL-C goals. As PCSK9 inhibitors have been shown to be effective in many patients with HoFH and have a good safety profile, it is reasonable to initiate this treatment next, if available. After assessing response to the addition of PCSK9 inhibitors, if LDL-C levels remain above goal, other options need to be explored. Among these are apheresis, lomitapide, and evinacumab, with the decision of which therapy to offer next depending on the availability of treatment and patient preference. Evinacumab, an ANGPTL3 inhibitor that was recently approved in Europe and the United States, has shown substantial LDL-C reduction that is independent of underlying LDLR function and comes with a favorable safety profile and good tolerability, all of which position this drug to become an integral part of the treatment regimen for patients with HoFH where available. Finally, early preclinical work in gene transfer and editing offers an exciting look toward the future landscape of treatment for patients with HoFH. As significant global disparities have been found in treatment and outcomes of HoFH[7], it will be important to ensure that these new therapeutic approaches are accessible to all patients with HoFH.

Conflict of Interest (COI)

MC reports research funding from Regeneron Pharmaceuticals and REGENXBIO; and honoraria from Amryt Pharma.

AB reports research funding from Amgen Inc., Ionis Pharmaceuticals, Novartis, Pfizer, and Regeneron Pharmaceuticals.

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