Targeted Therapies for Familial Hypercholesterolemia

Subjects: Medicine, General & Internal
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Several new targeted therapies were developed for familial hypercholesterolemia, and some are being tested to achieve the low-density lipoprotein (LDL)-C goals for high-/very-high-risk familial hypercholesterolemia (FH) patients as recommended by the ESC/EAS 2016–2019 guidelines. The advantage of targeted therapies is that they provide clinicians with the power to practice personalized or precision medicine with the aim of achieving better risk/benefit and cost/effectiveness of therapies.

Keywords: familial hypercholesterolemia ; atherosclerosis ; PCSK9

1. New Trends in Therapies for FH

Several new targeted therapies were developed, and some are being tested to achieve the low-density lipoprotein (LDL)-C goals for high-/very-high-risk familial hypercholesterolemia (FH) patients as recommended by the ESC/EAS 2016–2019 guidelines [1]. The mechanism of action and impact on LDL-cholesterol (LDL-C) plasma concentrations for both heterozygous and homozygous FH are shown in **Table 1**. The advantage of targeted therapies is that they provide clinicians with the power to practice personalized or precision medicine with the aim of achieving better risk/benefit and cost/effectiveness of therapies. This is important considering the elevated costs of monoclonal antibodies and RNA-targeted therapies.

Table 1. Mechanism of action and efficacy of approved therapies to treat familial hypercholesterolemia.

	Compound	Target	Mechanism of Action	Efficacy in Heterozygous FH (LDL-C Reduction)	Efficacy in Homozygous FH (LDL-C Reduction)
Statins	**Small molecule**	**HMG-CoA-reductase**	**Reduces cholesterol synthesis and VLDL production. Increases hepatic LDLR expression [2].**	**30–50% [3].**	**10–25% [4].**
Ezetimibe	**Small molecule**	**NPC1L1**	**Reduces intestinal cholesterol absorption and increases hepatic LDLR expression [2].**	**10–15% [3].**	**10–15% [4].**
Bempedoic acid	**Small molecule**	**ACL**	**Reduces cholesterol synthesis and VLDL production. Increases LDLR expression [5].**	**16.5% in a pooled group of FH and other hypercholesterolemia patients [5].**	**N.A.**
Lomitapide *	**Small molecule**	**MTP**	**Reduces VLDL synthesis [2].**	**N.A.**	**33–50% depending on the dose [6][7][8].**
Alirocumab &Evolocumab	**Monoclonal antibody**	**Circulating PCSK9**	**Reduces LDLR degradation [2].**	**50–60% [9][10] adults and 35–38% pediatric patients for evolocumab [11][12].**	**20–34% (depends on *LDLR* variant 0–50%) [10][13].**
Inclisiran	**Small-interfering RNAs**	**Hepatic PCSK9 synthesis**	**Reduces LDLR degradation [14].**	**44.3% reduction [15].**	**Study ongoing.**

	Compound	Target	Mechanism of Action	Efficacy in Heterozygous FH (LDL-C Reduction)	Efficacy in Homozygous FH (LDL-C Reduction)
Evinacumab *	**Monoclonal antibody**	**Circulating ANGPTL3**	**Possibly increases the removal of VLDL and IDL particles by LDLR independent pathways [16].**	**38.5–56% reduction depending on dose regimen and patient [17].**	**49% [18].**
Lipoprotein apheresis	**Device**	**Circulating LDL, Lp(a) and VLDL particles**	**Reduces pro-atherogenic apoB-100-containing lipoproteins LDL, Lp(a), and VLDL as well as pro-inflammatory biomarkers [19].**	**60–80% [9].**	**60–80% [9].**

Note: HMG-CoA hydroxy methyl glutaryl Coenzime A; NPC1L1- Niemann-Pick C1 Like 1; ACL-Adenosine triphosphate citrate lyase enzyme (ACL); MTP-Microsomal triglyceride transfer protein; PCSK9-proprotein convertase subtilisin/kexin type 9; ANPTL3-Angiopoietin Like 3 Protein); low-density lipoprotein receptor (LDLR)-LDL receptor; *LDLR*-LDL receptor gene; Lp(a)-lipoprotein(a); * approved only for homozygous FH.

2. PCSK9 Inhibitors

PCSK9 inhibitors are a new class of cholesterol-lowering drugs currently used as a third-line treatment for FH or for statin-intolerant or very-high- atherosclerotic cardiovascular disease (ASCVD)-risk patients. PCSK9 is an enzyme produced mainly in the liver that is secreted into the plasma and plays a critical role in LDL catabolism. LDL normally clears from peripheral blood as a complex with the LDLR that enters the hepatocyte [20]. PCSK9 binds the LDLR at the hepatocyte surface, reducing its recycling from cytoplasm to cell membrane and consequently diminishing LDL clearance [21]. A previous animal study demonstrated that mice overexpressing PCSK9 protein have decreased LDLR function and elevated plasma LDL-C, while PCSK9 knockout mice have increased LDLR activity and lower plasma LDL-C levels [22]. Studies in humans showed that gain- and loss-of-function variants in PCSK9 were associated with an FH phenotype [23] and lower LDL-C concentrations and ASCVD risk [24], respectively.

These findings formed the basis for the development of PCSK9 inhibitors, whose mechanisms, as the name suggests inhibits the activity of PCSK9 proteins via different mechanisms. Three different subclasses of PCSK9 inhibitors are discussed.

Human monoclonal antibodies against PCSK9 (PCSK9-mAb) primarily include alirocumab and evolocumab [10][13][25]. The primary mechanism of action of PCSK9-mAb is via their binding activity on PCSK9 in the plasma, thereby blocking PCSK9 from binding the LDLR. The latter means that more receptors are available for the binding of ApoB100-LDL (apolipoprotein B (*APOB*)) complex for the onward clearance of circulating LDL particles [2][26].

Alirocumab and evolocumab are indicated for homozygous and heterozygous FH patients who persist with elevated LDL-C despite the use of statins and ezetimibe therapies. They are administered subcutaneously in bimonthly doses of 75–150 mg for alirocumab or 140 mg for evolocumab or 300 mg and 420 mg, respectively, for alirocumab and evolocumab once monthly. A recent open-label, single-arm multicenter study by Santos et al. (TAUSSIG) [27] evaluated the safety and efficacy of evolocumab in 300 patients aged ≥12 years with HoFH (n = 106) and severe HeFH (n = 194) who at the time of enrolment were on stable lipid-lowering therapy. Patients were started on evolocumab (420 mg monthly and later to 420 mg bimonthly as needed) or 420 mg bimonthly if on lipoprotein apheresis. At 12 weeks of evolocumab treatment, LDL-C decreased by 59.8 mg/dL (21.2%) and 104.4 mg/dL (54.9%) in patients with HoFH and HeFH, respectively; effects were sustained during a median follow-up of 4.1 years. A total of 26% of patients on active apheresis (severe heterozygous FH only) had their blood-filtering therapy discontinued to LDL-C control, and the overall rate of CVD events was only 2.7%, suggesting cardiovascular benefit of the drug in comparison with historical controls. Adverse reactions occurred in 89.3% of patients, which included nasopharyngitis, influenza, upper respiratory tract infection and headache [27]. The latter, however, did not lead to drug discontinuation. In the same study, Raal et al. [28] demonstrated that in homozygous FH, the presence of *LDLR* null variants was associated with a lower or absent reduction in LDL-C with evolocumab in comparison with those with defective variants.

Blom et al. evaluated the effects of alirocumab in homozygous FH [29]. In a randomized, double-blind, placebo-controlled, parallel-group study, 69 patients on high-intensity lipid-lowering therapy including statins, ezetimibe, lomitapide and

apheresis were enrolled. Patients were randomized to receive 150 mg alirocumab treatment every 2 weeks (*n* = 46; baseline LDL-C = 295 mg/dL) or placebo (*n* = 23; baseline LDL-C = 259 mg/dL) for a duration of 12 weeks. Alirocumab significantly decreased LDL-C by 26.9% compared with 8.6% for placebo ($p < 0.0001$). Similar to evolocumab [27], alirocumab was generally well tolerated, with a safety profile comparable with that of placebo [29]. Both studies show that PCSK9-mAb may be useful for LDL-C reduction in either severe heterozygous or homozygous FH, although the efficacy in the latter is much less pronounced.

Evolocumab was approved for pediatric patients (older than 10 years) with HeFH based on results from the HAUSER trial [11]. In HAUSER, evolocumab (420 mg once a month) was administered in a randomized 2:1 double-blind fashion to 157 pediatric patients (mean age 13.7 years) who persisted with LDL-C > 135 mg/dL despite usual statin and/or ezetimibe therapy (mean baseline LDL-C 185 ± 45 mg/dL). After 24 weeks, there was a mean 38.3% reduction (−44.5% vs. −6.2%) in LDL-C versus placebo. Adverse events were similar in comparison with placebo, with nasopharyngitis and headache being the most frequent. Recently Santos et al. [12] have published the long-term open label follow-up of HAUSER. In that study, 150 patients received evolocumab and completed the open-label extension with a median follow-up of 80.3 weeks. The main study objective was safety and tolerability; treatment-associated adverse events occurred in 70% of study participants and were similar to the ones occurring in the randomized double-blind phase. No event led to treatment discontinuation, and no patient developed anti-drug antibodies. There were no adverse events related to growth, sexual maturation, neurocognitive function, glucose homeostasis, steroid hormones or liposoluble-vitamin blood concentrations. At week 80, the mean percentage change from baseline in LDL cholesterol was −35.3% (standard deviation 28.0). The study clearly shows that evolocumab can add LDL-C reduction to usual therapy in heterozygous FH, is safe and is well tolerated.

Small-interfering RNA (siRNA) technology is a novel approach to PCSK9 inhibition [14]. The siRNA technology deploys a small double-stranded RNA molecule of 19–23 nucleotides in size to induce the silencing of the target gene. The siRNA inclisiran is a novel PCSK9 inhibitor for the treatment of heterozygous FH and common hypercholesterolemia [14]. Inclisiran blocks the translation of PCSK9 messenger RNA, leading to its degradation by the RNA-induced silencing complex (RISC) andthereby decreasing the concentrations of intrahepatic and plasma PCSK9 [14][15]. Compared with PCSK9-mAbs, inclisiran has a more convenient dose regimen of 300 mg twice-yearly injections and could be useful for enhancing patient compliance. In a recent phase 3, double-blind trial by Raal et al. [15], 482 adult heterozygous FH patients were randomized to receive 300 mg of inclisiran (*n* = 241) or matching placebo (*n* = 241) and followed up for 540 days. The mean reduction in the LDL-C level from day 90 to day 540 was 38.1% in the inclisiran group, while there was an increase of 6.2% in placebo ($p < 0.001$), a −44.3% difference. The most frequent adverse events not differing from placebo were nasopharyngitis, influenza, upper respiratory tract infection and back pain. In a pilot study, Hovingh et al. [30] tested the feasibility of PCSK9 suppression with inclisiran in four homozygous FH patients. LDL-C changes varied from +3% to −37% in 180 days, and PCSK9 plasma levels were reduced by −48.7% to −83.6% at day 90 and by −40.2% to −80.5% at day 180. Their study paved the way for ORION 5 (NCT03851705) with a greater number of homozygous FH patients. However, results are not yet published.

At any rate, the infrequent dosing regimen and acceptable safety profile of inclisiran make it a suitable alternative to PCSK9-mAbs [15].

Oral PCSK9 inhibitors are being developed as an alternative to the subcutaneous PCSK9-mAbs and inclisiran. This presentation may be especially suitable for FH patients who cannot comply with subcutaneous injections of PCSK9-mAbs and inclisiran. MK-0616 is an orally bioavailable PCSK9 inhibitor and preliminary results from an ongoing phase I clinical trial by Johns et al. [31] were presented at the 2021 Scientific Sessions of the American Heart Association. Their study involved 60 healthy male volunteers and has demonstrated that MK-0616 (10–300 mg) was well-tolerated with no adverse effects. In the second phase of their study, involving 40 hypercholesterolemic patients (male and female), MK-0616 lowered baseline LDL-C levels by 65% after 14 days of treatment. Further data are, however, necessary.

Gennemark et al. [32] developed a chemically modified PCSK9 antisense oligonucleotide (ASO) for oral delivery. Preliminary results showed that the subcutaneous injection of 90 mg ASO reduced PCSK9 by >90% in patients with elevated LDL-C levels with a predicted 80% steady state with a 25 mg monthly maintenance dose [32]. When ASO was co-formulated with sodium caprate (a permeation enhancer) in an oral tablet form and administered to dogs, it resulted in 7% hepatic bioavailability, which was 5 times greater than that of plasma. Using prediction models, 15 mg/day of oral ASO should suppress PCSK9 in peripheral blood by 80% steady state and therefore be viable for oral formulation [32].

PCSK9 inhibitors are frequently prescribed as third-line treatment in patients who could not respond well or tolerate conventional lipid-lowering therapies. They are ideal for those with heterozygous FH [33]. However, despite the use of

high-dose statins and ezetimibe in combination with PCSK9 inhibitors, many patients with homozygous FH fail to achieve optimal reductions of LDL-C levels [34]. Thus, more treatment strategies are still needed.

3. Bempedoic Acid

Bempedoic acid (BA) is an oral inhibitor of cholesterol biosynthesis approved for cholesterol reduction [5]. Its mechanism of action involves the inhibition of the adenosine triphosphate citrate lyase (ACL), which acts upstream of HMG-CoA-reductase in the cholesterol biosynthesis pathway. A recent randomized controlled trial enrolled 2230 patients with ASCVD, heterozygous FH or both, all on the maximum tolerated dose of statin monotherapy (mean baseline LDL-C = 103.2 ± 29.4 mg/dL) to receive either BA treatment (n = 1488) or placebo (n = 742). During the 52 weeks of treatment, the incidence of adverse effects was comparable between the two groups. At week 12, the BA group exhibited significant LDL-C reduction from baseline (16.5%). At 52 weeks, BA did not result in higher incident of adverse effects and LDL-C lowering effects were maintained [35]. Similar results, a 21% reduction in LDL-C level compared with placebo, were reported after 12 weeks in another randomized study that evaluated BA in patients with hypercholesterolemia and statin intolerance [36]. These findings, in general, indicate that BA is efficacious and safe for lowering LDL-C in patients with hyperlipidemia including heterozygous FH patients.

4. Angiopoietin-like 3 Protein (ANGPTL3) Inhibitors

Angiopoietin-like 3 protein (ANGPTL3) is an endogenous inhibitor of lipoprotein and endothelial lipases. Loss-of-function variants of the ANGPTL3 gene are associated with lower serum cholesterol and triglyceride levels and a lower ASCVD risk [37]. Evinacumab, a human monoclonal antibody for ANGPTL3 inhibition (ANGPTL3-mAbs), was approved for the treatment of adults and pediatric patients older than 12 years with homozygous FH [17][18]. Raal et al. [18] showed in a randomized double blind study that 15 mg/kg infusions of evinacumab every 4 weeks reduced LDL-c by 49% at week 24 in comparison with placebo in homozygous FH patients (n = 65, baseline LDL-C of 255 mg/dL) undergoing maximal lipid-lowering therapies (statins, ezetimibe, PCSK9 inhibitors, lomitapide and/or lipoprotein apheresis). Of importance, and different, from PCSK9 inhibitors, evinacumab provided robust LDL-C reduction (−43.4%) even in patients with *LDLR* null variants. Adverse events did not differ from placebo. Animal models suggest that evinacumab increases the removal of VLDL (very-low-density lipoprotein) and IDL particles, precursors of LDL, by a non-LDLR related pathway [16].

In another double-blind, placebo-controlled, phase 2 trial, Rosenson et al. [38] enrolled 272 patients with and without heterozygous FH and with evidence of refractory hypercholesterolemia with atherosclerosis (LDL-C levels ≥ 70 mg/dL) or without atherosclerosis (LDL-c levels ≥ 100 mg/dL). Patients were randomly assigned to receive evinacumab at various dosing regimens (either subcutaneous or intravenous) or a placebo. After 16 weeks, evinacumab lowered LDL-C by 38.5–56% according to dose regimen compared with placebo, with low incidence of adverse effects (3–16%) across trial groups. Evinacumab is not yet approved for refractory heterozygous FH. Despite favorable results with monoclonal antibodies against ANGPTL3, recently, the development of an ASO against that protein, vupanorsen, was interrupted due to adverse liver events [39]. This clearly demonstrates that despite similar targets, different technologies vary when safety is concerned, and more clinical studies are warranted.

5. MTP Inhibitors

MTP is an enzyme essential for the assembly of VLDL in hepatocytes and chylomicrons in enterocytes. The inhibition of MTP blocks VLDL assembly and reduces LDL-C levels [2]. Lomitapide is an MTP inhibitor used as a lipid-lowering agent approved for the treatment of homozygous FH patients [6][8]. A previous single-arm, open-label, phase 3 multicenter study by Cuchel et al. [8] enrolled 29 homozygous FH patients to receive lomitapide in doses ranging from 5 to 60 mg/day depending on safety and tolerability. Lomitapide achieved a 50% reduction in baseline LDL-C levels at 26 weeks and maintained steady states of 44% and 38% at weeks 56 and 78, respectively. However, the drug produced gastrointestinal adverse effects and liver steatosis, though this did not result in discontinuation.

Two studies [6][7] have provided long-term efficacy and safety data on lomitapide in patients with homozygous FH treated up to 5.9 years. Blom et al. [6], in an extension of the original study by Cuchel et al. [8], showed in 17 patients followed up for 5.1 years that lomitapide in a 40 mg dose reduced LDL-C by 45% with hepatic safety. The most important reported adverse events were diarrhea, nausea, dyspepsia and vomiting. Underberg et al. [7] showed in the LOWER-registry that the median lomitapide dose of 10 mg provided a sustained 33% reduction in LDL-C after 5.9 years. In those who remained on lomitapide therapy until the end of follow-up, LDL-C reduction was 45%, with 65.4% and 41.1% achieving an LDL-C < 100 mg/dL or <70 mg/dL, respectively. Treatment-related adverse events occurred in 54.6%, and 23.2% of patients, who discontinued the therapy due to that. Gastrointestinal and hepatic events occurred, respectively, in 13.5%

and 15.1%. Overall, the studies reported consistent results demonstrating that lomitapide, when used in combination with other lipid-lowering therapies is effective in lowering LDL-C levels with an acceptable tolerability and safety profile [6][7].

Ben-Omran et al. [40] evaluated the effects of lomitapide (mean dose 24.5 ± 4.3 mg/day; during 20.0 ± 2.9 months) in a case series of 11 pediatric homozygous FH patients, mean age 11.6 ± 1.1 years and 64% males, undergoing statin and or ezetimibe therapy. LDL-C was reduced by 58.4 ± 6.8% from a baseline of 419 ± 74.6 mg/dL. The most frequent adverse events were nausea, vomiting and diarrhea but were well tolerated. A phase III study (NCT04681170) is testing the efficacy and safety of lomitapide in pediatric homozygous FH patients aged 5–17 years old with a duration of up to 80 weeks.

6. Gene Therapies

People affected by FH are ideal candidates for gene therapy, which is potentially the most definitive treatment for life. Possible gene therapies include CRISPR/Cas9 for heterozygous FH and viral vectors for homozygotes.

The Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)-Associated System 9 (Cas9) or simply CRISPR/Cas9 is the most promising genome editing tool for model systems including animal zygotes and human cells. CRISPR/Cas9 has useful applications in genetic research and is a promising tool for clinical applications in treating genetic disorders [41].

A recent in vivo animal study used a recombinant adeno-associated virus (AAV) vector carrying CRISPR/Cas9 gene editor (AAV-CRISPR/Cas9) and targeting an LDLR mutant mice model [42]. The mutant mice with loss of LDLR function exhibited severe atherosclerotic phenotypes when fed a high-fat diet. The AAV-CRISPR/Cas9-mediated gene editing partially corrected the point mutation in the LDLR gene expressed in hepatocytes and restored partial LDLR protein expression. The treatment significantly decreased total cholesterol, triglycerides, and LDL-c in the serum and, consequently, decreased the build-up of atherosclerotic plaques in the aorta. This finding shows that CRISPR/Cas9 is promising for the treatment of heterozygous FH.

A recombinant adeno-associated virus (AAV) vector carrying an *LDLR* transgene has been recently unveiled and is currently at phase 1/2a testing phase [43]. In animal studies, an LDLR-deficient mouse model ($Ldlr^{-/-}$, $Apobec1^{-/-}$ or double knockout—DKO) treated with AAV carrying an LDLR transgene at vectors doses as low as 3×10^{11} exhibited enhanced transgene expression and decreased serum LDL-C levels [44]. Findings from DKO mice indicate the potential of an AAV vector carrying an LDLR transgene to be used for the treatment of high-risk homozygous FH patients.

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