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EVINACUMAB, A NEW TREATMENT FOR FAMILIAL HYPERCHOLESTEROLAEMIA: MECHANISM OF ACTION, SAFETY AND EFFICACY

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ABSTRACT

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder characterized by extremely elevated low-density lipoprotein cholesterol (LDL-C) levels and a markedly increased risk of premature atherosclerotic cardiovascular disease. The aim of this review was to summarize current knowledge on the pathophysiology, diagnosis, and management of HoFH, with particular emphasis on angiopoietin-like protein 3 (ANGPTL3) inhibition and the clinical role of evinacumab. A comprehensive analysis of published clinical trials, guidelines, and observational studies was conducted to evaluate available diagnostic criteria and therapeutic strategies. Standard lipid-lowering therapies often fail to achieve recommended LDL-C targets in HoFH due to impaired LDL receptor function. Evinacumab, a fully human monoclonal antibody targeting ANGPTL3, has demonstrated substantial LDL-C reductions independent of LDL receptor activity in both adult and pediatric patients. Clinical studies report LDL-C reductions of approximately 45–50%, along with a favorable safety profile. In conclusion, ANGPTL3 inhibition with evinacumab represents a significant advancement in the treatment of HoFH, offering an effective therapeutic option for patients with inadequate response to conventional lipid-lowering therapies.

KEYWORDS

Evinacumab, ANGPTL3, Familial Hypercholesterolaemia, Lipid-Lowering Therapies, Atherosclerotic Cardiovascular Disease

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Abbreviations:
AAV – adeno-associated virus
ANGPTL3 - angiopoietin-like protein 3
ANGPTL4 - angiopoietin-like protein 4
ANGPTL8 - angiopoietin-like protein 8
ApoA-I - apolipoprotein A-I
ApoB - apolipoprotein B
ApoE - Apolipoprotein E
ASCVD - atherosclerotic cardiovascular disease
CCD - coiled-coil domain
CHO - Chinese hamster ovary
CI - Confidence Interval
CRISPR - clustered regularly interspaced short palindromic repeats
CT - computed tomography
CVD - cardiovascular disease
DNA - Deoxyribonucleic Acid
EAS - European Atherosclerosis Society
ECG - echocardiogram
EDTA - Ethylenediaminetetraacetic Acid
EL - endothelial lipase
EMA - European Medicines Agency
ERK - extracellular signal- regulated kinase
ESC - European Society of Cardiology
FDA - Food and Drug Administration
FFAs - free fatty acids
FH - familial hypercholesterolaemia
FLD - fibrinogen-like domain
HDL - high-density lipoprotein
HDL-C - high-density lipoprotein cholesterol
HeFH - Heterozygous Familial Hypercholesterolemia
HoFH - Homozygous Familial Hypercholesterolemia
IgG4 - Immunoglobulin G4
IV - intravenous
LA - lipoprotein apheresis
LDL - Low-Density Lippoprotein
LDL-C - Low-Density Lippoprotein-Cholesterol
LDLR - Low-Density Lippoprotein Receptor
LDLRAP1 - Low-Density Lipoprotein Receptor Adaptor Protein 1
LLT - lipid-lowering therapy
LOF - loss-of-function
Lp(a) - lipoprotein(a)
LPL - lipoprotein lipase
MAD - multiple ascending dose
MAPK - mitogen-activated protein kinase
MRI - magnetic resonance imaging
MTP - microsomal triglyceride transfer protein
OLTP - open-label treatment period
PCSK9 - proprotein convertase subtilisin/kexin type 9
SAD - single ascending dose
sHTG - severe hypertriglyceridemia
siRNA - small interfering RNA
STAP1 - Signal-Transducing Adaptor Protein 1
TC - Total Cholesterol
TGs - triglycerides
TRLs - triglyceride-rich lipoproteins
VLDL - Very Low-Density Lippoprotein

1. Introduction

Dyslipidemia can be perceived as a broad spectrum of metabolic disorders in which blood serum concentrations of lipids and lipoproteins exceed the desired levels **[1]**. The common Fredrickson classification of those pathologies is based on lipoprotein analysis by electrophoresis and ultracentrifugation, in which isolated LDL-C concentration elevation characterises class IIA **[2]**. Although in the ESC/EAS 2019 guidelines there has not been defined an explicit level of LDL-C above which hypercholesterolemia can be diagnosed, it is considered for LDL-C to be elevated if greater than or equal to 3 mmol/l (115 mg/dl) as lower values were considered target levels for those patients whose CVD risk is low **[3].** In a NATPOL 2011 study LDL-C ≥ 3 mmol/l has been found in 57,8% of adults aged 18 to 79 years with a domination of males (58,3%) over females (57,3%) **[4]**. Another study LIPIDOGRAM 2015 found the LDL-C concentration ≥ 3 mmol/l in 60% of Polish adults who sought medical care in primary health care practices **[5]**. Hypercholesterolemia can be further divided into primary (monogenic or polygenic) and secondary, mostly to other diseases or drug usage **[1]**.

FH is a genetically determined class IIA dyslipidemia characterized by very high LDL-C concentration and development of atherosclerosis from early childhood **[1,2]**. The main causes of FH are pathogenic variants in the genes encoding the LDLR (>90%), its ligand - ApoB (5%) or PCSK9 (<1%), while rarer causes (<<1%) include variants in genes encoding ApoE and STAP1 **[6,12]**. These variants are associated with autosomal dominant inheritance with gene-dosage effect. Because of its autosomal dominant inheritance, there are two forms of the condition: HeFH and HoFH. HoFH is classified as a rare disease, occurring from 1 in 160,000 to 1 in 300,000 cases **[10]**. The heterozygous form is much more common. According to prevalences between 1/500 and 1/200 worldwide, between 14 and 34 million individuals around the world have FH **[8]**. Based on a meta-analysis of six extensive observational studies, the estimated prevalence of FH in Poland is approximately 1 in 250 individuals between 20 and 79 years of age, with only 4–5% of affected individuals diagnosed **[9].** A less common autosomal recessive form of FH is associated with biallelic pathogenic variants in LDLRAP1 which encodes a protein required for clathrin-mediated internalization of the LDLR by liver cells **[13]**. In the remainder, a polygenic aetiology is most likely, due to the co-inheritance of common LDL-C-raising variants. Genetic testing is typically performed using DNA isolated from a peripheral blood sample collected in EDTA tubes. However, nucleic acids isolated from buccal swabs can also be used. While genetic testing is a dependable diagnostic method, it may not detect primary mutations in 20%-40% of FH cases **[6,7]**. The cardiovascular presentation and management of FH will differ between patients based on their underlying genetic factors **[14]**. The median LDL-C level is 206.3 mg/dl (5.4 mmol/l) and 558.6 mg/dl (14.7 mmol/l) in HeFH and HoFH individuals, respectively **[11]**. Xanthomas, most often found in Achilles tendons and finger extensors as well as corneal arcus, although rare, are characteristic clinical findings in FH. Other symptoms are indirect and include premature (<55 years in men and <60 years in women) signs of atherosclerosis, most often CVD **[1]**. During a study by Villa *et al.* **[20]** a CVD event rate ratio (FH patients versus non-FH patients) of 7.1 (95% CI: 5.7–8.7) was calculated. Thus, FH is often diagnosed late, frequently when clinical or subclinical atherosclerosis symptoms are already present. The average age of FH diagnosis in Poland is approximately 40 years for adults and around 9–10 years for children **[15]**.

The most used diagnostic tools in the pediatric population are: the framework developed by the Simon Broome Register Group and the Dutch Criteria, shown in Tables 1. and 2. respectively.

Table 1. Simon Broome Register Group Criteria as a diagnostic tool in FH **[16]**.

Criterion A	Total cholesterol levels > 290 mg/dl (> 7.5 mmol/l) in adults Total cholesterol levels > 260 mg/dl (> 6.7 mmol/l) in children aged less than 16 years or LDL-C > 190 mg/dl (> 4.9 mmol/l) in adults LDL-C >155 mg/dl (> 4.0 mmol/l) in children aged less than 16 years
Criterion B	Tendon xanthomas in the patient or tendon xanthomas in a first or second-degree relative
Criterion C	DNA-based evidence of an LDL-receptor mutation, familial defective Apo B-100, or a PCSK9 mutation
Criterion D	Family history of myocardial infarction before the age of 50 years in a second-degree relative or before the age of 60 years in a first-degree relative
Criterion E	Family history of elevated total cholesterol > 290 mg /dl (> 7.6 mmol/l) in an adult first or second-degree relative Family history of elevated total cholesterol > 260 mg/dl (> 6.7 mmol/l) in a child, brother, or sister aged 16 years or younger

Definite FH (criteria A and B or C met); possible FH (criteria A and D or A and E met).

Abbreviations: DNA: Deoxyribonucleic Acid; LDL-C: Low-Density Lipoprotein Cholesterol; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; ApoB: Apolipoprotein B

Table 2. The Dutch Criteria as a diagnostic tool in FH **[17]**.

1 point	First-degree relative with premature cardiovascular disease or LDL-C >95th percentile, or personal history of premature peripheral or cerebrovascular disease, or LDL-C between 155 and 189 mg/dL
2 points	First-degree relative with tendinous xanthoma or corneal arcus, or first- degree relative child (<18 years) with LDL-C >95th percentile, or personal history of coronary artery disease
3 points	LDL-C between 190 and 249 mg/dL
4 points	Presence of corneal arcus in patient age <45 years
5 points	LDL-C between 250 and 329 mg/dL
6 points	Presence of a tendon xanthoma
8 points	LDL-C >330 mg/dL or functional mutation in the *LDLR* gene

Premature: <55 years in men and <60 years in women

Definite FH (≥8 points); probable FH (6–7 points); possible FH (3–5 points).

Abbreviations: LDL-C: Low-Density Lipoprotein Cholesterol; LDLR: Low-Density Lipoprotein Receptor.

These criteria do not account for clinical CVD symptoms in the patient, which rarely appear in children with HeFH. FH is diagnosed in children based on phenotypic criteria, including elevated LDL-C levels and a family history of elevated LDL-C, premature coronary artery disease, and/or positive results of molecular testing. Children with TC levels ≥240 mg/dl (≥ 6.21 mmol/l) and LDL-C levels ≥160 mg/dl (≥ 4.14 mmol/l) have an elevated likelihood of being diagnosed with heterozygous FH **[18]**. In families where a pathogenic variant has been identified, children should undergo testing even if their lipid profiles appear normal. According to the current guidelines from the American Academy of Pediatrics **[19]**, it is recommended to conduct lipid profile screening in children over 2 years old whose parents have been diagnosed with FH and children over 2 years old with an unclear family history who present other risk factors, such as overweight, obesity, systolic and/or diastolic blood pressure readings between the 90th and 95th percentiles on three separate measurements, hypertension, diabetes, and low physical activity (<60 min daily).

2. Guidelines for treating homozygous familial hypercholesterolaemia

2.1 Management plan

Every newly identified patient with HoFH (homozygous familial hypercholesterolaemia) should be referred to a specialist centre at the diagnosis **[21]**. Because of the disease's severity, early testing needs to be extensive and should include Lp(a) (lipoprotein(a)) and comprehensive cardiovascular imaging **[21,22]**.

In order to identify disease burden, an ECG (echocardiogram) and low-dose CT (computed tomography) angiography are recommended **[21,23]**. It is advised for HoFH patients to receive CT angiography at least once after the age of 3, as it is crucial in differentiating between coronary ostial stenosis and aortic stenosis **[21]**. Follow-up CT angiographies should be performed as clinically needed **[21]**. HoFH patients should also receive echocardiography at the diagnosis and then annually after that **[21]**. Alternatively, high-resolution MRI (magnetic resonance imaging) has been shown to be able to detect atherosclerotic burden of the aorta, as well as thrombosis and lipid-rich carotid plaques **[21]**. Nonetheless, diagnostic tools such as tendon imaging, stress ECG, and coronary calcium scoring are not routinely recommended **[21]**.

2.2 Treatment pathways

Patients with familial hypercholesterolaemia (FH) are considered by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) to be either high risk, if they have FH without other major risk factors, or very high risk, if they have FH and ASCVD (atherosclerotic cardiovascular disease) or another major risk factor **[24]**. Therefore, the recommended LDL-C (low-density lipoprotein cholesterol concentration) goals are LDL-C < 70 mg/dL for high-risk patients and LDL-C < 55 mg/dL for very high-risk patients **[24]**. For the paediatric patients with HoFH, the recommended LDL-C is < 115 mg/dL, however, a lower goal is advised for children with an already established ASCVD **[24]**.

The ESC/EAS recommendations state that a combined lipid-lowering therapy comprising lifestyle modification, pharmacological therapy, and lipoprotein apheresis, should be started immediately after the diagnosis **[21,25,26]**. The ESC/EAS recommendations are described in Table 3 **[21]**.

Table 3. Recommendation for treatment of patients with homozygous familial hypercholesterolaemia by the European Atherosclerosis Society (EAS) and the European Society of Cardiology (ESC) **[21]**.

Recommendations for patients with homozygous familial hypercholesterolaemia
Patients should be under multidisciplinary care in specialist centres incorporating imaging, treatment, and comprehensive support.
It is recommended that patients should start lifestyle modifications and drug therapy combined with high-dose statin and ezetimibe at the diagnosis.
It is recommended that within 8 weeks of such treatment, a PCSK9-directed therapy should be considered if available. If a > 15% additional LDL-C reduction is achieved, PCSK9-directed therapy may be continued, otherwise, it should be stopped.
It is recommended that if LDL-C is above 115 mg/dL, novel therapies should be considered if available and affordable.
It is recommended that if LDL-C continuously exceeds 300 mg/dL, lipoprotein apheresis should be considered.
It is recommended that if novel therapies or lipoprotein apheresis are not available, liver transplantation should be considered.

Abbreviations: LDL-C: low-density lipoprotein cholesterol; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9.

Pharmacological therapy should be started as polytherapy, including high-dose statin and ezetimibe **[21]**. However, many patients may still require additional treatment **[21]**. Within the first 8 weeks of treatment, additional PCSK9 (proprotein convertase subtilisin/kexin type 9) therapy should be added if possible **[21]**. However, the efficacy of these interventions is determined by the patient's residual LDL (low-density lipoprotein cholesterol) receptor activity **[27]**. Yet, PCSK9 monoclonal antibodies such as evolocumab or alirocumab can still be very effective; if an HoFH patient shows an additional LDL-C reduction of over 15% after 1-2 doses, the PCSK9 therapy should be continued **[21,28-32]**. If the response to PCSK9 is poorer, the treatment may be stopped **[21]**. Nevertheless, for most HoFH patients, even with such polytherapy, the LDL-C will exceed the recommended levels **[21]**. In such cases clinicians should consider LDL receptor–independent therapies such as lipoprotein apheresis (LA), lomitapide, and angiopoietin-like protein 3 (ANGPTL3)-directed therapy **[21,27]**.

2.3 Therapies independent of low-density lipoprotein receptor function

2.3.1 Lipoprotein apheresis (LA)

Lipoprotein apheresis is a procedure in which cholesterol is extracorporeally removed from the blood **[33]**. LA can lower LDL-C by over 50% and thus, delay the development of ASCVD **[33-35]**. However, LDL-C returns to their previous levels in around 2 weeks after LA, which requires the patient to undergo the procedure very frequently **[36,37]**. LA is a crucial part of lipid-lowering therapy in patients with HoFH, mostly as an adjunctive **[38]**. The EAS and the ESC recommend that LA should be initiated promptly, in children by the age of 3, depending on appropriate venous access **[21]**. It is most vital in countries without access to newer types of treatment options **[21]**. Lipoprotein apheresis possesses a broad range of pleiotropic effects, it reduces the levels of pro-inflammatory mediators and improves myocardial perfusion **[39,40]**. Significantly, LA was found to be able to lower the levels of Lp(a), which is associated with a higher mortality rate in patients with HoFH **[39,41]**. Moreover, a study by Stefanutti *et al.* **[41]** has found that HoFH patients who received lipid-lowering therapy, including lomitapide and LA, had improved survival rates and coronary disease outcomes in comparison to patients who received standard lipid-lowering therapies, excluding LA and lomitapide. It has also been found that new medications such as lomitapide and evinacumab can help reduce the frequency of required LA **[21]**.

2.3.2 Lomitapide

Lomitapide is a microsomal triglyceride transfer protein inhibitor that works by stopping the creation of apoB-containing lipoproteins in the liver and intestines **[42]**. Studies have shown that an addition of lomitapide to a standard lipid-lowering therapy results in lowering LDL-C levels by around 60% and Lp(a) levels by around 15% **[43,44]**. A study by D'Erasmo *et al.* **[45]** has shown that long-term lomitapide leads to a significant reduction in LDL-C levels and a lesser need for lipoprotein apheresis. However, variability in response to the lomitapide poses a difficulty **[46]**. Studies have shown that some patients can be characterized as “hyper-responders” or “hypo-responders” depending on their gene mutation in microsomal triglyceride transfer protein (MTP), which is a protein that lomitapide directly binds to **[46-48]**. Moreover, another concern in long-term use of lomitapide is hepatic fat steatosis, the incidence of which seems to be increased as a result of lomitapide treatment **[49]**.

2.3.3 Evinacumab

Evanicumab is an angiopoietin-like protein 3 (ANGPTL3) monoclonal antibody, its efficacy, safety, and other characteristics are a main point of this article and are explained below **[21]**.

2.3.4 Liver transplantation

Liver transplantation may be a radical treatment option for the HoFH patients who are most affected by the disease, particularly young children with bi-allelic null variants **[21]**. Studies have shown that LDL-C levels normalise a few weeks after the transplantation, coronary artery disease outcomes seem to improve as well **[50-56]**. The EAS and the ESC recommend it as a last resort option, after careful consideration of its risks and benefits **[21]**.

2.4 Novel therapies for homozygous familial hypercholesterolaemia

There is still a great need for new therapeutic approaches for managing HoFH, especially for young children **[21]**. Gene-therapy seems to be promising, but more trials assessing its efficacy and safety are **[21]**. Studies about inclisiran, a small interfering RNA (siRNA) that targets PCSK9, have shown some unclear results regarding its effectiveness **[56,57]**. Zodasiran, an siRNA aimed at ANGPTL3, is being studied in a phase II trial with some positive results **[56,58,59]**. Several other agents that work via CRISPR (clustered regularly interspaced short palindromic repeats)-based gene editing are also being studied **[21]**. VERVE-201 is an agent targeting ANGPTL3, currently in preclinical studies, which has shown a 60% whole-liver editing and a 46% reduction in mean LDL-C in a study of non-human primates **[56,60]**. Another approach is adeno-associated virus (AAV)-mediated gene transfer, for example, AAV8-guided LDL-C transgene directed to the liver has been showing promising results and is currently undergoing 5 years of follow-up trial **[56,61]**.

3. ANGLPT3

Angioprotein-like protein 3 (ANGPTL-3) is a hepatic secretory glycoprotein belonging to the angioprotein-like family of proteins. It is encoded by the ANGPTL-3 gene on chromosome 1p31.3. It was originally identified in 1999 **[62]** and since then has been extensively studied.

3.1 the structure of ANGPTL-3

ANGPTL-3 is a 70-kDa glycoprotein comprising 460 amino acids. Its structure is characteristic for ANGPTLs family and includes a signal peptide, an N-terminal coiled-coil domain (CCD), a C-terminal fibrinogen-like domain (FLD) and a linker region. Each domain has separate specialized biological functions **[63]**.

The signal peptide, located at the extreme N-terminus, ensures directing ANGPTL3 into the secretory pathway - thanks to this mature proteins are released from hepatocytes into the bloodstream where they can perform their functions.

The N-terminal coiled-coil domain constitutes the main functional region responsible for the lipid metabolism as it inhibits lipoprotein lipase (LPL) and endothelial lipase (EL). This domain facilitates oligomerization, which is required for its full inhibitory activity and stability in circulation **[64]**.

Linker region connects CCD with FLD and contains conserved proprotein convertase cleavage site, which is needed for full inhibition activity of ANGPTL-3 **[65]**.

The FLD binds integrin αvβ3 on endothelial cells, activating signaling pathways that stimulate cell adhesion, migration, and blood vessel formation **[66]**. Furthermore, FLD takes part in lipolysis in adipocytes as it enhances the process without directly triggering lipolysis on its own. The effect is mediated by activation of the ERK/MAPK signaling pathway apart from the classical β-adrenergic signaling **[67].**

3.2 Role of ANGPTL3 in lipid metabolism

Studies have shown that loss-of-function (LOF) variants in the ANGPTL3 gene are associated with lower plasma levels of triglycerides (TGs), LDL cholesterol (LDL-C), and total cholesterol compared with non-carriers **[68]**. Individuals carrying such mutations present a phenotype called familial combined hypolipidemia which is characterized by panhypolipidemia (decreased level of TGs, LDL-C, HDL-C, apoB, and apoA-I) **[69]**. Moreover, LOF mutations in ANGPTL3 are associated with an approximately 34% reduction in the incidence of cardiovascular events among carriers **[70]**.

The primary role of ANGPTL3 in lipid metabolism is the inhibition of lipoprotein lipase (LPL), an enzyme responsible for the hydrolysis of triglycerides carried in chylomicrons and VLDL into free fatty acids (FFAs) and monoacylglycerol. By suppressing LPL activity, ANGPTL3 reduces the clearance of triglyceride-rich lipoproteins (TRLs), leading to increased plasma triglyceride concentrations **[71]**.

In addition to LPL, ANGPTL3 also inhibits endothelial lipase (EL), an enzyme involved in the hydrolysis of phospholipids in HDL particles. ANGPTL3 suppresses EL activity through a related mechanism involving its N-terminal domain **[72]**. As a consequence, phospholipid-rich HDL particles and plasma HDL-C levels are increased. ANGPTL3 has also been identified as a component of HDL, suggesting that it may modulate HDL function by influencing HDL protein composition **[73]**.

3.3 The cooperation between ANGTL3, ANGPTL4, ANGPTL8

ANGPTL-3 operates within the coordination with ANGPTL-4 and ANGPTL-8. The secretion of ANGPTL-4 and ANGPTL-8 depends on a nutritional state **[74]**. ANGPTL-8 is induced during the fed state. It works as a cofactor for ANGPTLL-3. Lacking the fibrinogen-like domain, in a liver it forms a complex with ANGPTL-3. Then the complex circulates and inhibits LPL in oxidative tissues such as heart and skeletal muscle, redirecting triglyceride-derived fatty acids toward adipose tissue for storage **[75]**. In adipose tissue, ANGPTL8 helps to regulate LPL activity by counteracting the inhibitory effects of ANGPTL4 and by reducing the influence of ANGPTL3–ANGPTL8–mediated LPL suppression in a tissue-specific manner. Studies show that loss of ANGPTL8 in the liver lowers plasma triglyceride levels, whereas loss of ANGPTL8 in adipose tissue increases triglycerides, indicating distinct roles of ANGPTL8 in different tissues **[76]**.

ANGPTL4 production is strongly increased during fasting and physical exercise. In adipose tissue, ANGPTL4 inhibits LPL by promoting its degradation, which limits triglyceride uptake into fat cells. As a result, fatty acids are redirected toward oxidative tissues such as the heart and skeletal muscle, where they are used for energy **[77]**.

The coordinated organization of ANGPTL-3-4-8 regulates LPL activity to ensure efficient usage of triglycerides between energy storage and utilization according to the organism's nutritional state. This interplay highlights the sophisticated molecular mechanisms underlying metabolic flexibility and overall energy homeostasis.

3.4 Strategies for ANGPTL3 inhibition

Since the therapeutic potential of blocking ANGPTL-3 was first recognized, several approaches have been explored. Our work focuses on Evinacumab, a monoclonal antibody, whose mechanism of action is discussed below. Apart from that, it is worth mentioning about RNA-based therapies that reduce ANGPTL-3 synthesis in hepatocytes - small interfering RNA agents such as zodasiran and solbinsiran **[78]**. Another approach involves antisense oligonucleotides targeting ANGPTL-3, such as vupanorsen, although their development has been limited because of the safety reasons **[79]**. The other strategies are aiming for ANGPTL-3-ANGPTL-8 complex instead of ANGPTL-3 expression alone **[80]** or gene-editing approach using CRISPR/Cas9 technology to permanently disrupt the ANGPTL-3 gene expression **[81]**. To sum up, there are ongoing efforts to translate ANGPTL-3 inhibition into safe and effective therapies, with multiple strategies currently under preclinical and clinical investigation. Among these, the most established approach, and the focus of this review, is evinacumab.

4. Characteristics of Evinacumab

4.1 Mechanism of Action

Angiopoietin-like protein 3 (ANGPTL3) is a key regulator of lipoprotein metabolism through inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL) **[82]**.

Evinacumab is a fully human monoclonal IgG4 antibody composed of two heavy chains and two kappa light chains **[83]**. Each heavy chain consists of 453 amino acids, while each kappa light chain contains 214 amino acids **[83]**. The heavy chains are linked by disulfide bonds, and each light chain is covalently bound to a heavy chain via disulfide bridges **[83]**.

Evinacumab exerts its therapeutic effect by binding to ANGPTL3, thereby preventing its inhibitory action on LPL and EL **[84,85,86]**. This results in reduced formation of remnant VLDL particles, which under physiological conditions are either cleared via the LDL receptor (LDLR) or converted into LDL particles during hydrolysis **[84,85,86]**. Newly formed LDL particles are subsequently removed through LDLR-mediated hepatic uptake **[84,85,86]**. In addition, evinacumab treatment leads to a reduction in plasma triglycerides (TG) and ApoB-containing lipoproteins **[87]**.

Inhibition of ANGPTL3 also enhances VLDL processing, promoting the generation of remnant particles with lower lipid content, which accelerates their clearance from the circulation **[84,85,86]**. Genetic studies have demonstrated that individuals carrying loss-of-function mutations in the ANGPTL3 gene exhibit significantly lower levels of LDL-C, TG, and HDL-C, along with a substantially reduced risk of ASCVD **[87]**. In familial hypercholesterolemia (FH), impaired LDLR function results in defective hepatic clearance of LDL particles and elevated plasma LDL-C levels **[82]**. Importantly, because evinacumab indirectly reduces remnant VLDL particles, its lipid-lowering effect is independent of LDLR activity **[84,88]**.

This LDLR-independent mechanism was investigated in a phase 2 trial (NCT02265952) involving lymphocytes isolated from patients with homozygous familial hypercholesterolemia (HoFH). Administration of evinacumab did not alter LDLR activity, confirming that its efficacy is not mediated through this receptor **[89,90]**.

This mechanism provides a novel therapeutic approach for patients with HoFH, enabling not only reduction of LDL-C levels but also attenuation of LDL precursors **[84,88]**. In addition to its effect on LDL-C, evinacumab enhances triglyceride hydrolysis, leading to a further reduction in plasma TG concentrations **[84,88]**.

Currently, evinacumab is commercially available as *Evkeeza*, manufactured by Ultragenyx **[83]**.

4.2 Pharmacokinetics and Pharmacodynamics

As a monoclonal antibody, evinacumab exhibits a characteristic concentration–time profile with both linear and nonlinear, target-mediated elimination **[84]**. This pharmacokinetic behavior has been observed in both healthy volunteers and patients with HoFH **[84]**. The primary efficacy endpoint guiding pharmacokinetic (PK) and pharmacodynamic (PD) analyses was the change in LDL-C concentration, while total ANGPTL3 levels served as a biomarker of target engagement **[84]**. Following intravenous administration of evinacumab at a dose of 15 mg/kg every 4 weeks, steady-state minimum serum concentrations were achieved after four

doses, with an accumulation ratio of approximately 2.0 **[84,91]**. Population PK analyses estimated the steady-state volume of distribution to be approximately 4.7 L **[84,91]**.

A pooled analysis by Dingman et al. **[84]** demonstrated that systemic exposure to evinacumab decreased with increasing age across all age groups, consistent with lower body weight under weight-based dosing regimens. PK/PD simulations were conducted for IV dosing schedules of 5 mg/kg and 20 mg/kg administered every 4 weeks **[84]**. The 5 mg/kg regimen was associated with markedly reduced therapeutic efficacy, whereas the 20 mg/kg dose did not provide clinically meaningful benefits beyond those observed with 15 mg/kg **[84]**.

Based on PK and PD findings, the optimal therapeutic dose of evinacumab for hypercholesterolemia was established as 15 mg/kg administered intravenously every 4 weeks **[84]**.

Cytochrome P450 enzymes and hepatic transporters do not play a role in evinacumab metabolism, thereby limiting the potential for pharmacokinetic drug–drug interactions **[87]**. Consequently, evinacumab may be safely combined with other lipid-lowering agents, including statins, ezetimibe, and PCSK9 inhibitors **[87]**. However, interactions with immunosuppressive agents, antidiabetic drugs, and other monoclonal antibodies remain insufficiently characterized, and further studies are required **[87]**.

4.3 Adverse Effects of Evinacumab

Evinacumab has been well tolerated by patients with no particular differences between the use of the drug and placebo and contributed to a noticeable lowering drop in LDL-C level **[82]**. The most common adverse effects presented were nasopharyngitis, headache, influenzalike illness, urinary tract infection, nausea and dizziness **[92,93].** During this randomized clinical trial investigation some serious side effects appeared such as carotid artery stenosis, coronavirus infection, chest pain, joint effusion, pulmonary embolism, gastrointestinal motility disorder, gallbladder polyp and atrial fibrillation, however, they have not been linked to the use of evinacumab. All of these symptoms occurred in only 9 of 94 patients, with each patient presenting only one adverse effect **[82]**.

4.3 Clinical Efficacy

4.3.1 Clinical trials and studies

In clinical trials evaluating evinacumab, the primary efficacy endpoint was the percentage change in LDL-C concentration **[84]**. Baseline LDL-C values were compared with levels measured at week 24 of treatment **[84]**.

In the phase 3 trial (NCT03399786), evinacumab was administered at a dose of 15 mg/kg intravenously every 4 weeks to both adults and adolescents aged ≥12 years. A total of 65 patients with HoFH were enrolled **[84,94]**. At week 24, LDL-C levels were reduced by 47.1% from baseline in the evinacumab group **[84]**. In contrast, patients receiving placebo experienced a 1.9% increase in LDL-C, resulting in a between-group difference of −49.0 percentage points ($P < 0.001$) **[84,85]**. LDL-C reduction was evident as early as week 2 and was sustained throughout the 24-week treatment period **[84]**.

Long-term efficacy and safety were further evaluated in study NCT03409744, in which LDL-C reduction at week 24 reached −43.7% **[84,95]**. Similar results were observed in a pediatric HoFH population enrolled in trial NCT04233918, with a mean LDL-C reduction of −48.3% **[84,96]**. Evinacumab is currently approved for use in children aged 12 years and older **[21]**. Beyond lipid lowering, evinacumab has demonstrated potential cardiovascular benefits. In an analysis comparing event-free survival in patients with HoFH treated with evinacumab (OLE ELIPSE HoFH; n = 12) with an untreated HoFH cohort (REFERCHOL; n = 21), no cardiovascular events were reported during 3.5 years of follow-up in the evinacumab group **[97]**. In contrast, 13 cardiovascular events occurred in 5 patients in the control cohort over a 4-year observation period **[97]**. These events included myocardial infarction, unstable angina, acute coronary syndrome, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) **[97]**. LDL-C levels in the evinacumab-treated group were reduced by 56% from baseline and remained consistently lowered throughout the study period **[97]**.

Long-term efficacy and safety were also assessed in a phase 2 open-label trial (NCT03175367) conducted by Rosenson et al. **[82,98]**. During a 72-week open-label treatment period, 96 patients with refractory hypercholesterolemia received evinacumab at a dose of 15 mg/kg IV every 4 weeks **[82]**. Treatment resulted in mean reductions in total cholesterol (−42.6%), ApoB (−38%), and LDL-C (−48.4%), while the median reduction in fasting triglycerides reached −57.2% **[82]**.

4.3.2 Comparison within races – white and japanese

A randomized study by Harada-Shiba et al. investigated the influence of ethnicity on the lipid-lowering effects of evinacumab, enrolling equal numbers of Caucasian and Japanese participants **[99]**. At week 8, LDL-C reduction was greater in Caucasian participants than in Japanese participants at the 15 mg/kg dose, whereas no such difference was observed at the 5 mg/kg dose **[99]**. Similarly, triglyceride reduction was more pronounced in Caucasian participants compared with Japanese participants for both intravenous dosing regimens **[99]**.

4.3.3 Effects on Triglycerides

The triglyceride-lowering effects of evinacumab were evaluated in phase 1 SAD and MAD studies (NCT01749878 and NCT02107872) **[100-102]**. In the SAD cohorts, 83 participants received single ascending doses of evinacumab administered subcutaneously (75, 150, or 250 mg) or intravenously (5, 10, or 20 mg/kg). A dose-dependent reduction in triglyceride levels was observed, with a maximal reduction of 76.9% on day 3 following IV administration of 10 mg/kg **[100]**. In the MAD cohorts, evinacumab was administered subcutaneously at doses of 150/300/450 mg weekly or 300/450 mg biweekly, or intravenously at 20 mg/kg every 4 weeks. The greatest triglyceride reduction (83.1%) was observed on day 2 following IV administration of 20 mg/kg every 4 weeks **[100]**.

A randomized phase 2 trial (NCT03452228) evaluated evinacumab in patients with severe hypertriglyceridemia (sHTG) **[93,103]**. Patients were stratified into three cohorts based on the presence and type of mutations in the LPL pathway. The median percentage reduction in triglycerides at week 12 was significantly lower in patients with biallelic loss-of-function mutations (27.7%) compared with those with heterozygous mutations (64.8%) or no detectable LPL pathway mutations (81.7%) **[93]**. Treatment effects were sustained through week 24 **[93]**.

4.4 Pregnancy and breastfeeding

An important consideration in the clinical use of evinacumab is its administration in pregnant or breastfeeding women **[91]**. Preclinical studies in animal models have demonstrated potential fetal toxicity, including malformations occurring during organogenesis **[91]**. The risk associated with breastfeeding remains insufficiently characterized; however, due to the high molecular weight of evinacumab (146 kDa), its transfer into breast milk is expected to be minimal **[91]**. Furthermore, it is anticipated that the immunoglobulin may undergo degradation in the neonatal gastrointestinal tract, resulting in reduced absorption and limited systemic exposure in the infant **[91]**. Although data from human studies are currently unavailable, patients should be informed of the potential risks associated with the use of evinacumab during conception attempts and while breastfeeding **[91]**.

4.5 Comparison with Other Lipid-Lowering Therapies

In patients with HoFH receiving intensive lipid-lowering therapy (LLT) consisting of high-intensity statins, ezetimibe, and PCSK9 inhibitors, the introduction of evinacumab represents a significant therapeutic advance **[86]**. Due to dysfunctional LDLR activity in HoFH, conventional LLT agents often fail to achieve adequate LDL-C reduction, as their efficacy depends largely on intact LDLR function **[86]**. In contrast, evinacumab enables effective LDL-C lowering even in patients with null–null LDLR variants through its LDLR-independent mechanism of action **[86]**.

Given the strong association between elevated LDL-C levels and cardiovascular morbidity and mortality, the use of evinacumab in patients with inadequately controlled hypercholesterolemia or HoFH may substantially reduce cardiovascular risk and improve long-term outcomes **[86]**. In an ongoing clinical trial (NCT03409744), mean changes in low-density lipoprotein cholesterol (LDL-C) concentrations at week 24 of therapy were evaluated according to age, sex, race, null versus non-null genetic variants, history of lipoprotein apheresis, concomitant use of ezetimibe, PCSK9 inhibitors, statins, and lomitapide, as well as baseline lipoprotein(a) [Lp(a)] levels **[86]**. Comparison of LDL-C percentage reduction by evicunamb depending on the subgroup is shown in Table 4.

Table 4. Comparison of LDL-C percentage reduction by evicunamb depending on the subgroup.

Subgroup	Category	Mean LDL-C Change
Age	<18 years	55,4%
	≥18 years	41,7%
Sex	Male	37,1%
	Female	51,2%
Race	White	41,8%
	Non-white	48,0%
LDLR variant	Null-null	49,0%
	Non-null	41,4%
Lipoprotein apheresis	Yes	39,0%
	No	46,3%
Ezetimib	Yes	47,1%
	No	27,5%
PCSK9 inhibitor	Yes	46,1%
	No	39,5%
Statin	Yes	43,3%
	No	48,1%
Lomitapide	Yes	52,3%
	No	41,7%
Baseline Lp(a)	<75 nmol/l	45,0%
	≥75 nmol/l	42,2%

Abbreviations: PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; Lp(a): Lipoprotein(a) **86]**.

A network meta-analysis conducted by Ling Zhang *et al.* evaluated the efficacy and safety of novel lipid-lowering agents, including alirocumab, evolocumab, inclisiran, and evinacumab, compared with placebo in patients with severe hypercholesterolemia **[104]**. Outcomes included reductions in LDL-C and total cholesterol, increases in HDL-C, and the incidence of adverse events **[104]**. The results are shown in Table 2.

Table 5. Results of network meta-analysis evaluated the efficacy and safety of novel lipid-lowering agents.

	LDL-C	HDL-C	Total Cholesterol	Adverse Events
Alirokumab	71,4%	68,2%	64,0%	26,2%
Evinacumab	44,3%	/	/	98,9%
Evolokumab	87,0%	81,8%	86,0%	15,2%
Inclisiran	47,2%	/	/	59,6%
Placebo	0,01%	0,03%	0,04%	50,0%

Abbreviations: LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol **[104]**.

The analysis demonstrated that evinacumab primarily reduced LDL-C without significantly affecting HDL-C or total cholesterol levels **[104]**. Although evolocumab provided the most pronounced improvements in lipid parameters, evinacumab exhibited a favorable safety profile. Nevertheless, substantial heterogeneity among the included studies underscores the need for large, multicenter randomized controlled trials to confirm these findings **[104]**.

Conclusions

Familial hypercholesterolemia (FH) is a genetically determined dyslipidemia marked by very high LDL-C levels and early-onset atherosclerosis. It is most often caused by pathogenic variants in LDLR (>90%), less commonly in ApoB or PCSK9, and is usually inherited in an autosomal dominant manner. FH occurs as heterozygous (HeFH) or the rarer homozygous form (HoFH), with HoFH affecting about 1 in 160,000–300,000 individuals. In Poland, FH prevalence is estimated at about 1 in 250 adults, yet only 4–5% of cases are diagnosed. A rare autosomal recessive form is linked to LDLRAP1 variants, and many cases have a polygenic basis. Median LDL-C levels are about 206 mg/dl in HeFH and about 559 mg/dl in HoFH. Clinical signs such as tendon xanthomas and corneal arcus are characteristic but uncommon, while premature CVD is a major consequence. FH patients have a markedly increased risk of cardiovascular events and are often diagnosed late (around age 40 in Polish adults). Diagnosis in children relies mainly on phenotypic criteria and family history, as clinical cardiovascular symptoms are rare. The Simon Broome Register Group and Dutch Lipid Clinic Network criteria are the most commonly used diagnostic tools. Genetic testing supports diagnosis, but its sensitivity is low. Current guidelines recommend lipid screening in children over 2 years old with a family history of FH or with additional cardiovascular risk factors and cascade testing in families with known pathogenic variants.

Patients with HoFH should be treated under multidisciplinary care in specialist centres. Treatment should be started immediately after the diagnosis and should include lifestyle modifications and drug polytherapy. Regarding medication, it is recommended that patients should be started on high-dose statin and ezetimibe therapy. Within 8 weeks of such treatment, a PCSK9-directed therapy should be added, and if it results in a > 15% additional LDL-C reduction, it shall be continued long-term. If LDL-C goals are not achieved with standard therapy, an additional therapy in the form of lomitapide and angiopoietin-like protein 3 (ANGPTL3)-directed therapy should be considered. If LDL-C continuously exceeds 300 mg/dL, lipoprotein apheresis should be considered. Liver transplantation is a last resort treatment option for most affected HoFH patients.

Current therapeutic options for homozygous familial hypercholesterolemia (HoFH) are limited due to its reliance on functional LDL receptors and are often associated with treatment burden and side effects. Evinacumab represents a new and promising therapeutic approach, leading to great LDL-C reduction through an LDL-receptor-independent mechanism. Evinacumab is a fully human monoclonal IgG4 antibody that exerts its therapeutic effect by binding to ANGPTL3. ANGPTL-3 is a hepatic secretory glycoprotein whose domain-specific structure enables coordinated inhibition of lipoprotein lipase and endothelial lipase, thereby controlling plasma triglyceride levels and the metabolism of LDL and HDL particles. Evidence from studies of LOF (loss of function) mutations shows that reduced ANGPTL3 activity leads to a favorable lipid profile and lower cardiovascular risk, highlighting its pivotal role in lipid homeostasis and therapeutic potential.

Evinacumab inhibits ANGPTL3, thereby neutralizing its inhibitory action on lipoprotein lipase (LPL) and endothelial lipase (EL). As a result, evinacumab enhances triglyceride hydrolysis, reduces remnant very-low-density lipoprotein (VLDL) particles, and leads to a significant reduction in low-density lipoprotein cholesterol (LDL-C). Importantly, its lipid-lowering effect is independent of low-density lipoprotein receptor (LDLR) activity, which distinguishes evinacumab from many existing lipid-lowering therapies.

Based on pharmacokinetic and pharmacodynamic findings, the optimal therapeutic regimen of evinacumab has been established as 15 mg/kg administered intravenously every four weeks. Numerous clinical trials have consistently demonstrated its efficacy in lowering LDL-C levels and suggest a potential reduction in cardiovascular risk, particularly in patients with refractory hypercholesterolemia. Studies show that evinacumab is generally well-tolerated and represents an effective adjunctive treatment option for both adults and children with HoFH. Despite these promising results, further research is warranted to address unresolved issues, including the safety and efficacy of evinacumab during pregnancy and breastfeeding. As a relatively novel therapeutic agent, evinacumab represents a highly anticipated advancement in the management of resistant hypercholesterolemia, offering a modern treatment option for patients both with and without underlying LDLR disorders.

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