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Inhibition of angiopoietin-like 3 for the management of severe hypercholesterolemia

Farzahna Mohamed, Theunis C. Botha, and Frederick J. Raal

Purpose for review
Despite the therapeutic advances for patients with severe hypercholesterolemia, particularly those with homozygous familial hypercholesterolemia (HoFH), most patients are unable to achieve target low-density lipoprotein cholesterol (LDL-C) levels with the current available standard lipid-lowering therapy (LLT). We review the role of angiopoietin-like 3 (ANGPTL3) inhibition as an additional therapeutic option for severe hypercholesterolemia, particularly HoFH.

Recent findings
Evinacumab is a monoclonal antibody against ANGPTL3, and reduces LDL-C independent of LDL-receptor activity. ANGPTL3 inhibitors are effective in lowering LDL-C in patients with FH, with a 50% reduction in LDL-C in those with HoFH. Longer-term efficacy and safety have been demonstrated with reductions in LDL-C maintained following 48 weeks of therapy. Gene silencing strategies directed against ANGPTL3 include antisense oligonucleotide and small-interfering ribonucleic acid (siRNA). ARO-ANG3 is a siRNA directed against ANGPTL3 messenger ribonucleic acid and is associated with up to a 42% reduction in LDL-C.

Summary
With the promise of these emerging novel therapeutics directed against ANGPTL3 on the horizon, achieving acceptable target LDL-C levels in HoFH without the need for lipoprotein apheresis may finally be a realistic goal and we can anticipate a decrease in cardiovascular morbidity and mortality in these difficult to treat patients.

Keywords
angiopoietin-like 3 deficiency, angiopoietin-like 3 inhibitor, familial combined hypolipidemia, familial hypercholesterolemia

INTRODUCTION

Severe hypercholesterolemia, defined as having an untreated low-density lipoprotein cholesterol (LDL-C) of greater than 190 mg/dL (4.9 mmol/L), occurs in 7% of adults in the United States, with an FH causing mutation sequenced in approximately 2% [1]. At any given LDL-C level, FH mutation carriers have a greater risk for atherosclerotic cardiovascular disease (ASCVD) than those without a mutation. When compared to a reference group without a mutation that has an LDL-C < 130 mg/dl (3.4 mmol/L), those with an LDL-C > 190 mg/dl (4.9 mmol/L) with no mutation have a sixfold increased risk of ASCVD and a 22-fold increased risk is observed in those with an FH causing mutation [1]. Current guidelines recommend a LDL-C of <70 mg/dL (< 1.8 mmol/L), if not < 55 mg/dL (< 1.4 mmol/L) in these high-risk patients because of increased risk for ASCVD as a result of lifelong exposure to elevated LDL-C levels [2]. Achieving these targets can be challenging despite the use of maximally tolerated doses of high potency statins even if used in combination with ezetimibe and a proprotein convertase subtilisin-kexin type 9 inhibitor (PCSK9i). Response to statins and PCSK9i therapy requires residual LDL-receptor (LDL-R) function and hence the addition of a drug that acts via an LDL-R independent pathway, should prove to be of benefit, particularly in patients with homozygous familial hypercholesterolemia (HoFH). Inactivation of angiopoietin-like 3 (ANGPTL3)

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KEY POINTS

- Evinacumab is a fully human ANGPTL3 blocking monoclonal antibody.
- Evinacumab reduces LDL-C by 50% or more even in patients with HoFH.
- The reduction in LDL-C with evinacumab is similar irrespective of the LDL-R function or background LLT.
- Gene silencing strategies include antisense oligonucleotide (ASO) and siRNA directed against ANGPTL3 are also under development.

lowers LDL-C via an LDL-R independent pathway and is thus a favorable approach in the treatment of HoFH. However, the exact mechanism of LDL-C reduction with ANGPTL3 inhibition remains uncertain.

ANGIOPOIETIN-LIKE 3 AND ITS ROLE IN LIPOPROTEIN METABOLISM

ANGPTL3 is produced in the liver and together with ANGPTL-4 and ANGPTL-8 help to regulate plasma lipoprotein metabolism [3]. Via its inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL), ANGPTL3 reduces hydrolysis of triglycerides (TG) particularly in muscle and fat tissue [4,5]. ANGPTL3 inhibits LPL by multiple mechanisms such as suppression of its catalytic activity and dissociation of LPL dimers into inactive monomers at high concentrations [6,7]. Together with furin and paired basic amino acid-cleaving enzyme 4, ANGPTL3 cleaves LPL which cause dissociation of LPL from the cell surface [8].

Proposed mechanism of low-density lipoprotein-cholesterol reduction with angiopoietin-like 3 inhibition

The reduction in TG and high-density lipoprotein cholesterol (HDL-C) with ANGPTL3 inhibition is attributed to disinhibition of LPL and EL activity, respectively [9▪▪,10]. Although, the exact mechanism of LDL-C reduction with ANGPTL3 inhibition in HoFH, particularly those with minimal or no residual LDL-R activity (null-null HoFH), remains uncertain, possible mechanistic roles of ANGPTL3 inhibition in lowering LDL-C have been postulated. These include a reduction in hepatic very-low-density lipoprotein (VLDL) production, alteration in LDL particle clearance or modulation of LDL-C production via upstream VLDL processing [9▪▪]. However, new research shows that EL-mediated processing of VLDL for LDL-R independent clearance is critical and that VLDL remnant clearance via receptor or nonreceptor mediated mechanisms is the most likely mechanism of LDL-C reduction (Fig. 1) [9▪▪].

Genetic inactivation of angiopoietin-like 3

Familial combined hypolipidaemia: angiopoietin-like 3 deficiency

The ANGPTL3 gene is located on chromosome 1 (1p31.1-p22.3). Loss-of-function (LOF) alleles encoding ANGPTL3 have been identified in patients with low plasma TG and other lipoproteins [11,12,13]. The first LOF mutations in humans were originally identified in a single family of European decent and described in 2010 [11]. Many different LOF mutations have since been identified based on population-based genome sequencing. Familial combined hypolipidaemia (FHBL2, OMIN #605019) is characterized by low plasma levels of VLDL-C, LDL-C, HDL-C, apolipoprotein B (apoB), apolipoprotein A1, TG and free fatty acids (FFA) [14]. LOF mutations in ANGPTL3 have been identified as the cause for this hypolipidemic phenotype [11]. Both homozygote and heterozygote carriers of mutant ANGPTL3 alleles display a phenotype associated with reductions in all lipoproteins compared to patients with normal alleles with homozygotes having a more pronounced phenotype than heterozygotes [14].

Angiopoietin-like 3 and cardiovascular risk

In view of ANGPTL3's role in lipoprotein metabolism, its role as a risk factor for ASCVD has been investigated. Early studies suggested a positive correlation between ANGPLT3 levels and carotid artery intimal wall thickness after adjusting for other traditional risk factors such as age, sex, smoking, and cholesterol levels [15]. Recent data from the Brisighella Heart Study Group also suggest that ANGPTL3 levels are a predictor of atherosclerosis in the peripheral vasculature when using indirect measures such as the ankle-brachial index (ABI). After adjusting for age and LDL-C, multivariate analysis on the whole study population showed that ANGPTL3 levels were one of the main predictors of ABI [16].

In a study evaluating atherosclerotic plaque size in patients that survived a first myocardial infarction, those carrying certain single-nucleotide polymorphisms in the ANGPTL 3 gene promotor region had larger plaque areas [17].

Not only is there evidence to suggest that ANGPTL3 is associated with an increased risk of ASCVD but recent studies also suggest that ANGPTL3 deficiency, or the presence of LOF mutations in the ANGPTL3 gene, offers protection from ASCVD. These findings are consistent with other studies, and a

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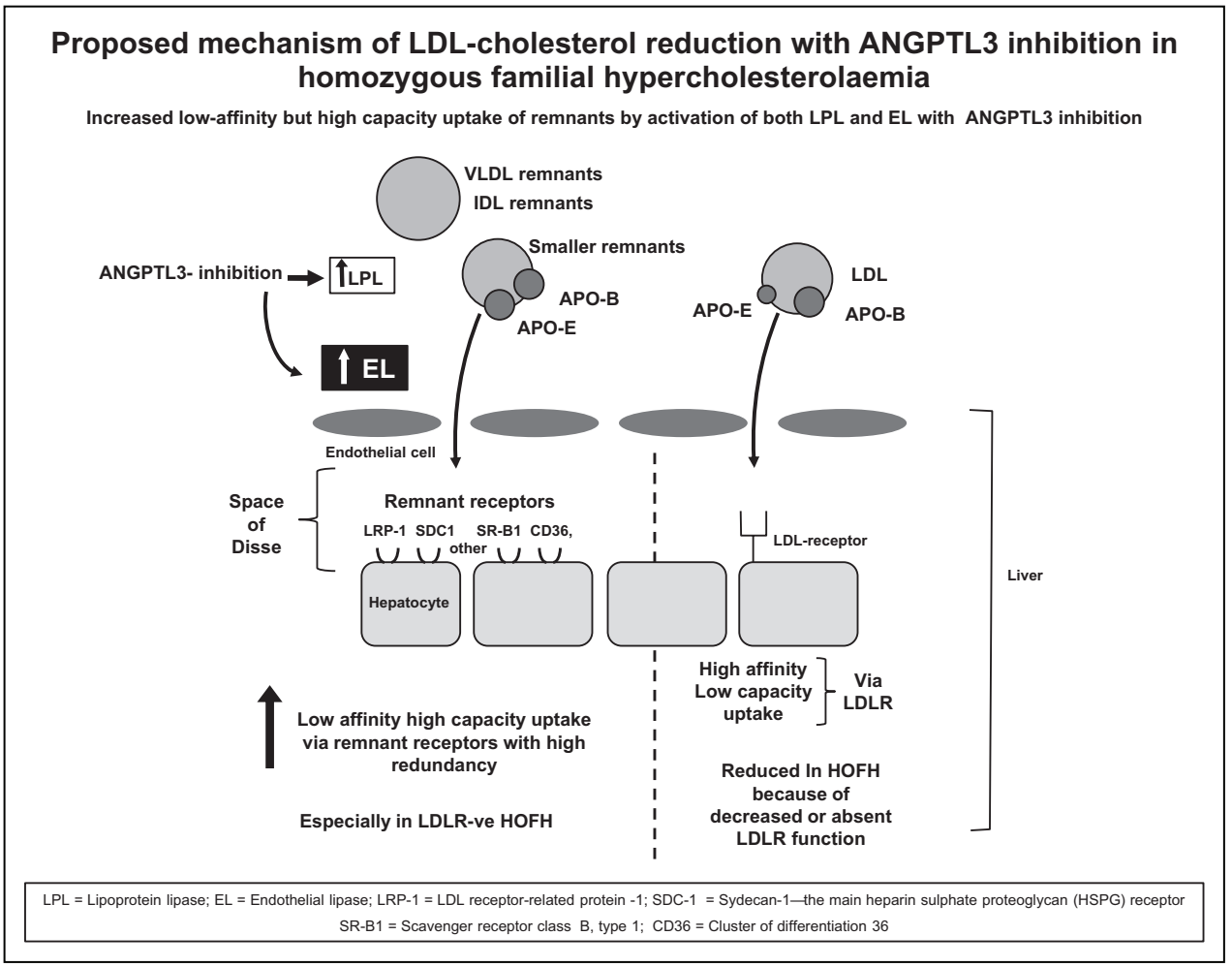

FIGURE 1. Proposed mechanism of LDL-C reduction with ANGPTL3 inhibition. Inhibition of ANGPTL3 reduces VLDL lipid content and size, and generates remnant particles that are removed from the circulation. Endothelial lipase is the key mediator of this LDL-R independent pathway. Multiple hepatic remnant receptors could contribute to remnant clearance including LRP-1, SDC-1, SR-B1, CD36, and other un-identified receptors. However, nonreceptor mediated clearance mechanisms as well as extrahepatic expression of these remnant receptors could potentially contribute to remnant clearance. Clearance of these remnant particles leads to depletion of the LDL precursor pool, thus restricting LDL-C production and reducing LDL-C levels. Modification of VLDL by EL is critical for clearance via an LDL-R independent pathway and whilst EL is dispensable for LDL-C in normal individuals, the EL-dependent alternative pathway is more critical when LDL-R activity is minimal or absent. *Adapted from Ref. [9▪▪]. ANGPTL3, angiopoietin-like 3; EL, endothelial lipase; LDL-C, low-density lipoprotein cholesterol; LDL-R, LDL-receptor; VLDL very-low-density lipoprotein.

meta-analysis by Stitziel *et al.* evaluating 21980 patients with coronary artery disease (CAD) and 158200 control subjects, showed that LOF mutations in the ANGPTL 3 gene had a 34% lower risk of CAD, with lower circulating ANGPTL 3 levels being associated with a lower odds ratio of having a myocardial infarction [18]. Analysis from participants in the UK Biobank, EPIC Interact, and EPIC Norfolk also suggest that LOF mutations in ANGPLT3 offer greater protection from CAD than other LDL-C lowering genetic mechanisms [19].

Thus, data from preclinical studies and human genetic analyses have shown a reduction in LDL-C and TG-rich lipoproteins, both of which are implicated in ASCVD. Dewey *et al.* evaluated the relationship between ANGPTL3 deficiency and ASCVD and observed a 41% lower odds for CAD as compared to the general population [20]. This led to the development of targeted medical therapy against ANGPTL3 and includes both monoclonal antibodies and small-interfering ribonucleic acid (siRNA) to ANGPTL3.

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Pharmacological inactivation of angiopoietin-like 3 – clinical translation

Angiopoietin-like 3 directed therapy: monoclonal antibodies directed against angiopoietin-like 3 – evinacumab

In the phase 1 trial, conducted by Dewey and colleagues, using evinacumab, a fully human ANGPTL3-blocking monoclonal antibody, in healthy adults, with a fasting TG level 150–450 mg/dl (1.7–5.1 mmol/L) or an LDL-C level of $\geq$ 100 mg/dl (2.6 mmol/L), a dose-dependent reduction in fasting TG up to 76% and LDL-C of up to 23% was demonstrated [20].

A proof-of-concept phase 2 study, involving nine patients with genotypically confirmed HoFH, showed that Evinacumab was associated with a mean LDL-C reduction of 49% at week 4 [10]. This reduction in LDL-C also occurred in those HoFH patients with minimal or no residual LDL-R function (null–null HoFH) suggesting a mechanism of action independent of the LDL-R [10]. This was further confirmed on functional analysis of LDL-R activity in lymphocytes, whereby evinacumab had no effect on LDL-R activity [21]. A reduction was also seen in apoB, non HDL, TG, and HDL-C levels [10].

Raal and colleagues report the results of the much anticipated ELIPSE HoFH phase 3 trial, assessing the efficacy and safety of evinacumab in HoFH. In this trial, 65 patients with HoFH, with an LDL-C > 70 mg/dl (1.8 mmol/L) despite lipid-lowering therapy (LLT) with or without lipoprotein apheresis, were randomized to receive an intravenous infusion of evinacumab 15 mg per kilogram (mg/kg) body weight or placebo every 4 weeks [22▪▪]. Approximately 63% of patients were on at least three lipid modifying drugs, with 77% on a high-intensity statin, 75% on ezetimibe, 77% on a PCSK9i, 25% on lomitapide, and 34% on lipoprotein apheresis [22▪▪]. A significant reduction of 47% in LDL-C was seen at 24 weeks in those receiving evinacumab, with a marked decrease in LDL-C starting from as early as two weeks post the first dose of evinacumab. The reduction in LDL-C was similar irrespective of background LLT and was similar in those receiving lipoprotein apheresis. Almost 50% of patients receiving evinacumab achieved an LDL-C < 100 mg/dl (< 2.6 mmol/L) and up to 30% achieved an LDL-C < 70 mg/dl (< 1.8 mmol/L). A reduction in LDL-C from baseline of $\geq$ 50% was seen in 56% of patients. Of the 65 patients included in the trial, 53 patients (82%) had genetically confirmed HoFH, with 35% having null–null LDL-R variants (defined as < 15% residual LDL-R activity). A greater reduction in cholesterol was seen in those on evinacumab as compared to placebo regardless of the LDL-R activity, with a 43.4% reduction in those with null-null LDL-R variants and 49.1% reduction in those with non-null LDL-R variants. Furthermore, in a post hoc analysis of 8 patients with < 2% functional LDL-R activity, evinacumab showed a between group mean difference of 72.3% in LDL-C [22▪▪]. A reduction in other lipid parameters was seen, with a between group difference of 50% in TG, and 37% in apoB [22▪▪]. There were no major safety concerns with adverse events being similar in those receiving evinacumab or placebo.

Trial results were recently published comparing subcutaneous to intravenous evinacumab conducted in 272 patients with or without heterozygous FH (HeFH), who had refractory hypercholesterolemia, defined as an LDL-C > 70 mg/dl (> 1.8 mmol/L) and clinical ASCVD or an LDL-C > 100 mg/dl (>2.6 mmol/L) without ASCVD despite PCSK9i therapy. Unfortunately, a minority, only 44%, were also on maximally tolerated high-intensity statin therapy with or without ezetimibe. At week 16, the between group difference in LDL-C in the subcutaneous regimens of evinacumab were significantly lower compared to placebo with 450 mg weekly, 300 mg weekly, and 300 mg every two weeks subcutaneous dosing reducing LDL-C by −56%, −52,9% and −38.5% respectively ($P < 0.001$). The intravenous regimens of evinacumab at a 4 weekly dose of 15 mg/kg body weight and 5 mg/kg as compared to placebo, showed a -50.5% and -24.2% between group difference in LDL-C respectively. Significant dose-dependent reductions in all atherogenic lipoprotein levels except for lipoprotein(a) were also seen [23▪].

Reduction in HDL-C was approximately 30% at the maximum subcutaneous and intravenous dose [23▪]. Treatment with evinacumab in the ELIPSE HoFH trial showed a 29.6% reduction in HDL-C [22▪▪].

The clinical implications of this reduction of HDL-C as well as LDL-C on ASCVD risk is unknown, and although the clinical trials with evinacumab reported so far were not designed to assess its effect on ASCVD risk reduction, the DiscovEHR study is reassuring in that it showed that participants with heterozygous LOF variants in ANGPTL3 had decreased levels of all three major lipid parameters and atherogenic lipoproteins including TG, HDL-C, LDL-C and apoB with a significantly lower odds of ASCVD [20]. Furthermore, the significant reduction in LDL-C levels associated with evinacumab potentially translates into CVD benefit as supported by genetic data [22▪▪,23▪,24,25].

Longer term safety and efficacy of evinacumab has been shown in the open-label period of the phase 3 ELIPSE HoFH trial, whereby a mean LDL-C reduction of 46.3% was observed at week 48 with

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no serious adverse events ascribed to treatment with evinacumab [26]. The reduction in LDL-C was similar irrespective of the LDL-R function or background LLT [26,27▪]. Furthermore, the reduction in LDL-C with evinacumab is also comparable in different ethnic groups, whereby a similar reduction in LDL-C was observed between Japanese and Caucasians [28].

Antisense oligonucleotide to angiopoietin-like 3 – angiopoietin-like 3-L_{RX}

Therapeutic RNA gene silencing differs from monoclonal antibody therapy, as it targets messenger ribonucleic acid (mRNA) to block protein synthesis instead of blocking protein function [29▪]. Within the clinical phase of dyslipidemia, there are two methods of gene silencing using antisense oligonucleotide (ASO) or siRNA technology [29▪].

Graham and colleagues evaluated the effect of an ASO against ANGPTL3 mRNA in 44 healthy adults, with TG levels > 90 mg/dl (1 mmol/L) or LDL-C > 70 mg/dl (1.8 mmol/L) as compared to placebo. The drug was administered subcutaneously as a single dose (20,40, or 80 mg) or multiple doses (10, 20, 40, 60 mg), for six weeks [30]. Participants receiving the subcutaneous injection at a dose of 60 mg or greater per week had a mean reduction in TG levels of 50%, LDL-C of 33% and HDL-C of 27%, on day 43, which was significantly greater than placebo [30,31]. There was also a 22% reduction in the atherogenic apoB. No serious adverse events were reported [30].

Small-interfering RNA to angiopoietin-like 3 – ARO-ANG3

ARO-ANG3 (Pharmaceutical company developing the drug is Arrowhead Pharmaceuticals, Inc) is an siRNA directed against ANGPTL3 mRNA [32▪]. Results from the ongoing phase 1 study investigating ARO-ANG3 in 22 patients with hypercholesterolemia on LLT, with or without ezetimibe and a PCSK9i, showed a mean reduction in LDL-C of up to 42% and a mean maximum reduction in TG of 79–88% in five patients with hyper-TG [32▪].

CONCLUSION

Despite major advances in the field of ASCVD, lipid lowering therapeutic strategies have not been successful in all patients, especially those with HoFH. Based on robust genetic and clinical evidence, ANGPTL3 inhibition epitomizes a new era in the treatment of severe hypercholesterolemia. Evidence suggests that achieving target LDL-C early and aggressively is beneficial against ASCVD and thus these novel agents pave the way for a promising future in lipid management and the prevention of ASCVD. Achieving acceptable target LDL-C levels in HoFH patients without the need for lipoprotein apheresis may finally become a reality.

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Conflicts of interest

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