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Review article

Angiopoietin-like protein 3 inhibitors and their effects on hyperlipidemia and atherosclerotic risk

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Angiopoietin-like protein 3 (ANGPTL3) has emerged as an important regulator of lipid metabolism. Current innovative therapeutic options using monoclonal antibodies, antisense oligonucleotide or vaccine approaches to block this protein may reduce the atherosclerosis risk in individuals with dyslipidemia. This review aimed to discuss the effectiveness of these new ANGPTL3 inhibitors. Currently, evinacumab and vupanorsen are effective ANGPTL3 inhibitors. These drugs are used to treat patients with hyperlipidemia. Moreover, both drugs were associated with a significant reduction in triglyceride and low density lipoprotein levels and may prevent the development of atherosclerosis.

Keywords: ANGPTL3, inhibitor and atherosclerosis.

Abnormally high levels of density lipoprotein (LDL) and triglyceride (TG) in the blood are associated with hypercholesterolemia and hypertriglyceridemia (HTG), respectively. Hypercholesterolemia causes premature coronary heart disease and stroke [1] and HTG results in acute pancreatitis [2] and cardiovascular disease (CVD).[3, 4] Thus, a target to reduce abnormally high LDL and TG levels is sought to more efficiently prevent heart disease, stroke, and pancreatitis

Angiopoietin-like protein 3 (ANGPTL3) is a 460 amino acid (aa) glycoprotein that is secreted predominately by the liver. ANGPTL3 contains an N-terminal region predicted to be intrinsically disordered, a coiled-coil region and a C-terminal fibrinogen-like domain. [5] The structure of the *ANGPTL3* gene is shown in **Figure 1**. An N-terminal fragment of ANGPTL3 with the coiled-coil domain, which is involved in binding and inhibiting lipoprotein lipase (LPL) and hepatic lipase (HL), is produced after the protein is cleaved and glycosylated. Meanwhile, a C-terminal fibrinogen-like domain, a 16-aa signal peptide are required for secretion [6] and are involved in the angiogenesis. This feature is similar to the function of angiopoietins [7, 8]

ANGPTL-3 regulates serum lipid levels by inhibiting the enzymatic activity of LPL and HL. Lipases hydrolyze triacylglycerols found in lipoproteins and chylomicrons into non-esterified free fatty acids (FFA) and monoacylglycerols. Silencing ANGPTL3 increases the LPL/HL, which leads to increase lipolysis and serum lipid clearance by the liver and other organs, leading to hypolipidemia. However, ANGPTL3 overexpression decreases LPL/HL levels, enhances circulating lipoproteins and leads to hyperlipidemia **(Figure 2).**

ANGPTL3 has various loss of function (LOF) or decrease of function mutations. Many of them are frameshifts or premature stop codons, whereas others are caused by single aa changes in the C-terminal. Tikkanen E, *et al.* reported that *ANGPTL3* homozygotes with the p.S17X mutation exhibited considerably greater LPL activity. [9] Furthermore, a study of two Spanish patients with familial hypobetalipoproteinemia discovered a homozygous deletion of 5 base pairs at codon 121 of *ANGPTL3*, (p.N121Lx2), which results in a shortened protein with 122 residues, These traits include low plasma levels of LDL and TG. Importantly, Dewey FE, *et al.* analyzed 45,226 individuals and found that carriers of an LOF mutation in *ANGPTL3* had approximately 30.0% lower circulating TG levels and 10.0% lower circulating LDL levels than no carriers. Of the 13,102 patients with CVD, those with an LOF mutation in *ANGPTL3* had 40.0% reduced risk for major adverse cardiovascular events. In the myocardial infarction genetics consortium trials, Stitziel NO, *et al* analyze 20,092 individuals and found that noncarriers of an LOF mutation in *ANGPTL3* had 11.0% lower total cholesterol, 12.0% lower LDL, and 17.0% lower TG to levels than noncarriers.

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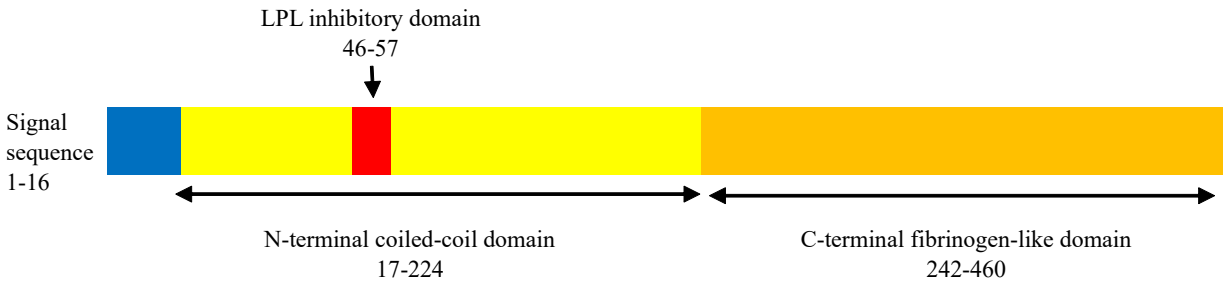

Figure 1. The structural of *ANGPTL3* gene.

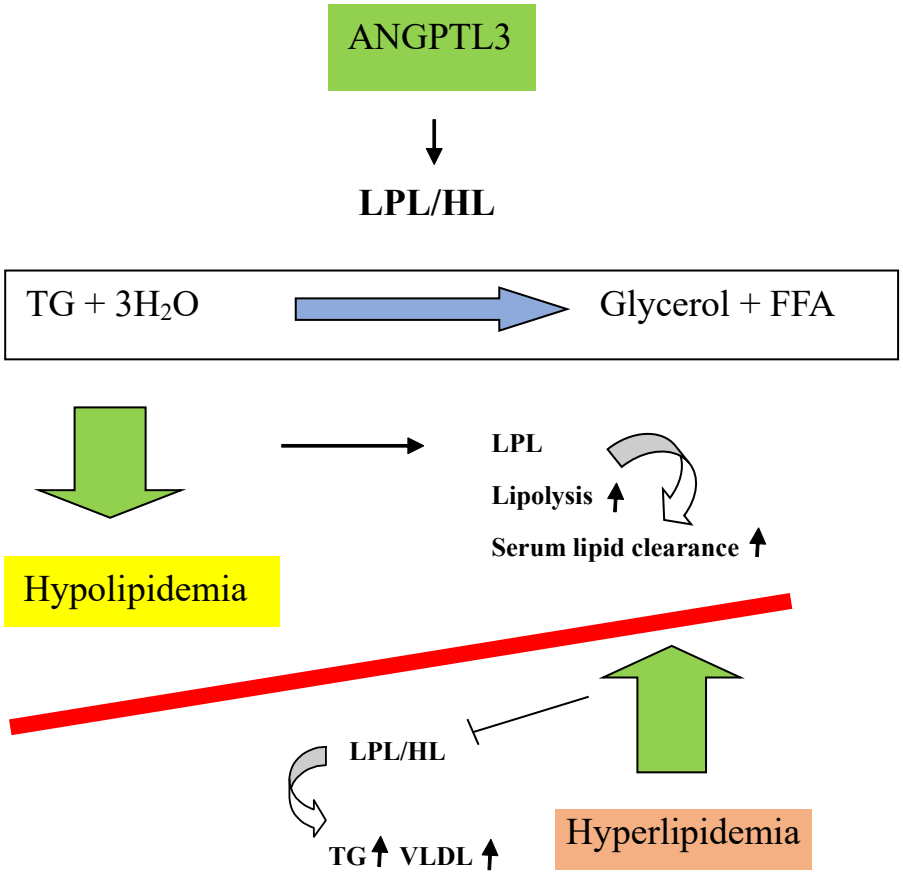

Figure 2. The function of ANGPTL3 in lipid metabolism.

Biterova E, *et al.*[5] identified crystal structures of 12 reported point mutations (p.M259T, p.R288Q, p.S292P, p.E375K and p.Y417C, p.Y344S, p.G253C, p.I333S, p.D290H, p.C408R, p.Y250C and p.T383S) in the C-terminal domain to explain why these mutations cause functional loss. Four of the mutations, p.S292P, p.R288Q, p.E375K and p.Y417C abolish or severely reduce secretion *in vitro* implying that they significantly affect the folding and/or stability of *ANGPTL3*. LOF mutations in *ANGPTL3* have been linked to a lower total atherosclerosis risk and plaque accumulation in humans. ANGPTL3 inhibitor therapy is therefore one way to prevent heart disease and stroke more efficiently.

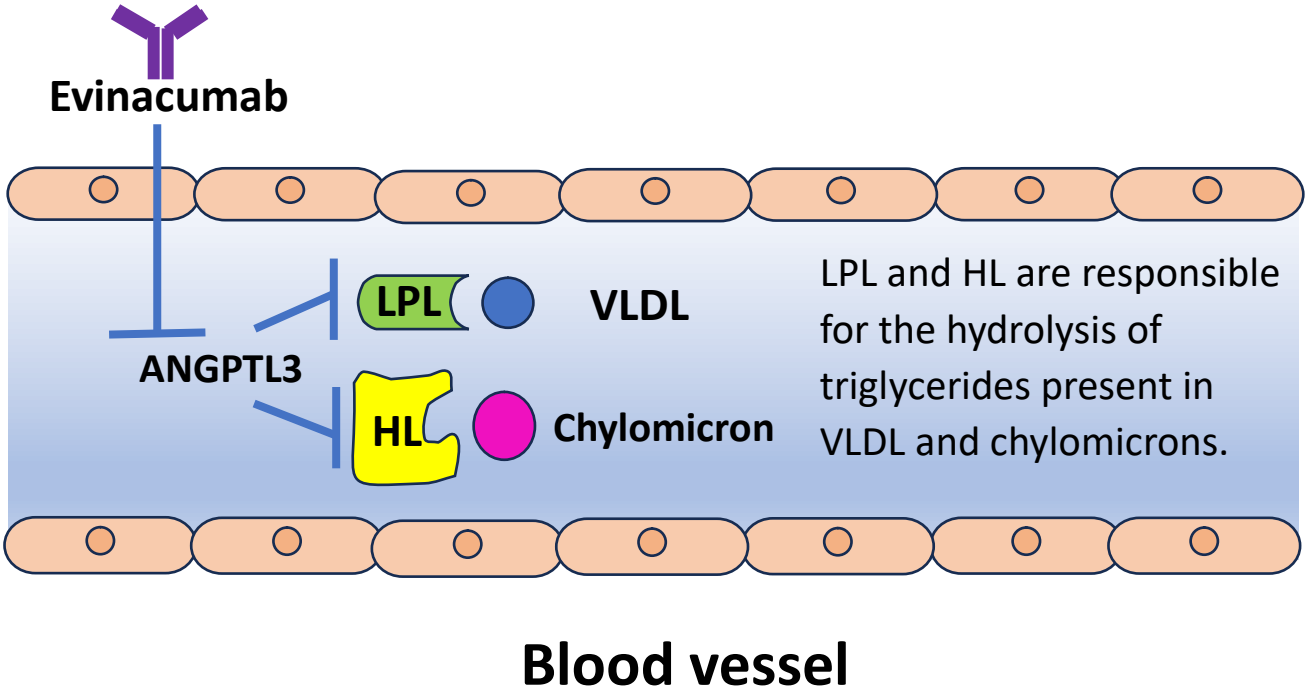

Figure 3. Mechanism of action of evinacumab.

ANGPTL3 inhibitors

Monoclonal antibody-(mAb)-based therapy

Evinacumab is a completely human IgG4 mAb that selectively inhibits ANGPTL3 in the circulation [10], resulting in ANGPTL3 deficiencies, activation of both LPL and HL activities [11], and decreases in plasma TG and LDL levels. The mechanism of action and summary of the studies of evinacumab are shown in **Figure 3 and Table 1,** respectively.

In patients with high TG levels, evinacumab was well tolerated and decreased triglycerides by up to 80.0% within a short period.[10] Ahmad Z, *et al.* [10] examined participants with TG levels > 150 but ≤ 450 mg/dL and LDL ≥ 100 mg/dL (n = 83 for the single ascending dose study [SAD]; n = 56 for the multiple ascending dose study [MAD]) and randomized them 3:1 evinacumab: to placebo. The SAD group received evinacumab subcutaneously (SC) at 75/150/250 mg or intravenously at 5/10/20 mg/kg, and their progress was monitored until day 126. The MAD group received evinacumab at 150/300/450 mg once weekly, 300/450 mg every 2 weeks, or intravenously at 20 mg/kg once every four weeks until day 56, with a 6-month follow-up. Both trials showed dose-dependent reductions in TG levels, with a maximal decrease of 76.9% at day 3 with 10 mg/kg intravenously in the SAD group and 83.1% at day 2 with 20 mg/kg intravenously once every 4 weeks in the MAD group.

Rosenson RS, *et al.* [12] examined the effectiveness of evinacumab in patients with severe HTG (sHTG). This phase 2 trial evaluated evinacumab in three cohorts of patients with sHTG: cohort 1, familial chylomicronemia syndrome with homozygous LOF LPL pathway mutations (n = 17); cohort 2, multifactorial chylomicronemia syndrome with heterozygous loss-of-function LPL pathway mutations (n = 15); and cohort 3, multifactorial chylomicronemia syndrome without LPL pathway mutations (n = 19). Fifty-one patients were randomized 2 : 1 to intravenous evinacumab 15 mg/kg or placebo every 4 weeks for a 12-week double-blind treatment, followed by a 12-week single-blind treatment. In cohort 3, the median percent reduction in TG levels was - 68.8%; and the absolute median change was - 905 mg/dL, whereas cohorts 1 and 2 had less change. This study suggested that evinacumab was effective in reducing TG levels in patients with sHTG without LPL pathway mutations.

Table 1. Results of the studies of evinacumab.

Study	Design	Intervention	Results
Rosenson R, *et al.* [12]	Phase 2 trial (NCT03452228 , three cohorts of patients with severe HTG: cohort 1, familial chylomicronemia syndrome with bi-allelic loss-of-function lipoprotein lipase (LPL) pathway mutations (n = 17); cohort 2, multifactorial chylomicronemia syndrome with heterozygous loss-of-function LPL pathway mutations (n = 15); and cohort 3, multifactorial chylomicronemia syndrome without LPL pathway mutations (n = 19).	Intravenous evinacumab 15 mg /kg or placebo every four weeks.	Evinacumab reduced triglycerides in cohort 3 by a mean (standard error, SE) of -27.1% (37.4).
Fachin A, *et al.* [15]	A case of 10-year-old boy who presented hypertriglyceridemia, with a pre-treatment triglyceride level of 1,341 mg/dL.	Evinacumab at a dose of 15 mg/kg every four weeks.	Blood triglyceride levels reduced reaching 154 mg/dL in 24 hours. The drug was well-tolerated, and the boy continued the inpatient treatment three months, maintaining triglyceride levels below 350 mg/dL.
Raal FJ, *et al.* [13]	double-blind, placebo-controlled, phase 3 trial, 65 patients with homozygous familial hypercholesterolemia	Intravenous evinacumab 15 mg /kg or placebo every four weeks.	Patients in the evinacumab group had a relative reduction from baseline in the LDL level of 47.1%, as compared with an increase of 1.9% in the placebo group. The LDL level was lower in the evinacumab group than in the placebo group in patients with null-null variants (- 43.4% *vs.* + 16.2%) and in those with non-null variants (- 49.1% *vs.* - 3.8%). Adverse events were similar in the two groups.
Weigman A, *et al.* [17]	The phase 3 study, 14 patients 5 to 11 years of age with genetically proven HoFH (true homozygotes and compound heterozygotes) with LDL-C >130 mg/dL, despite optimized lipid-lowering therapy	Evinacumab at a dose of 15 mg/kg every four weeks.	LDL level decreased with a mean (SE) of -48.3% (10.4%) from baseline to week 24.

Table 1. (Cont.) Results of the studies of evinacumab.

Study	Design	Intervention	Results
Shamsudeen I, ***et al.*** [16]	A 17-year-old boy was diagnosed with severe HoFH due to compound heterozygous *LDLR* pathogenic variants.	Evinacumab at a dose of 15 mg/kg every four weeks.	After 12 months, his time-averaged LDL decreased by 53.4% from 338.4 mg/dL to 157.8 mg/dL.
Stefanutti C, ***et al.*** [14]	Seven patients with genetically confirmed HoFH.	Evinacumab at a dose of 15 mg/kg every four weeks.	Twenty-four months of treatment with evinacumab resulted in a significant reduction in LDL -46.8%.
Ahmad Z, ***et al.*** [10]	Subjects with triglycerides > 150 but ≤ 450 mg/dL and low-density lipoprotein cholesterol ≥ 100 mg/dL (n = 83 for single ascending dose study (SAD); n = 56 for multiple ascending dose study (MAD).	SAD subjects received evinacumab subcutaneously (SC) at 75/150/250 mg, or intravenously at 5/10/20 mg/kg. MAD subjects received evinacumab subcutaneously at 150/300/450 mg once weekly, 300/450 mg every 2 weeks, or intravenously at 20 mg/kg once every 4 weeks.	Dose-dependent reductions in triglycerides were observed in both studies, with maximum reduction of 76.9% at day 3 with 10 mg/kg intravenously in the SAD and of 83.1% at day 2 with 20 mg/kg intravenously once every 4 weeks in the MAD.
Harada-Shiba M, ***et al.*** [18]	Double-blind, placebo controlled, Phase I, 96 healthy Caucasian and Japanese participants.	evinacumab subcutaneous (SC) 300 mg single dose, SC 300 mg once weekly for eight doses, intravenous (IV) 5 mg/kg, or IV 15 mg/kg once every 4 weeks for two doses.	The safety profile of evinacumab (IV and SC) in both ethnicities was comparable with placebo. Evinacumab injections produced significant reductions in LDL and TG levels both in Japanese and Caucasian subjects. Dose-related reductions in LDL and triglycerides were observed with evinacumab in both ethnic groups.

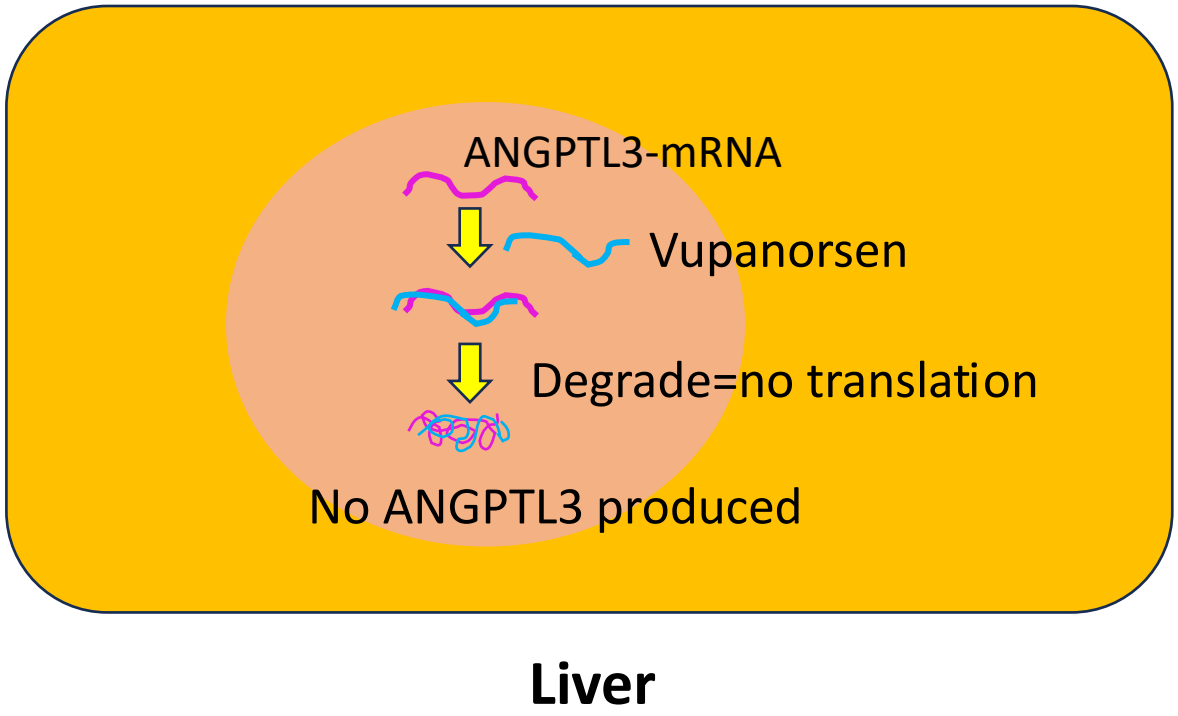

Figure 4. Mechanism of action of vupanorsen.

In a double-blind, placebo-controlled (phase 3) study [13], 65 patients with homozygous familial hypercholesterolemia (HoFH) who were receiving stable lipid-lowering treatment were randomly assigned to receive evinacumab intravenously (15 mg/kg of body weight) every 4 weeks or placebo. At week 24, the evinacumab group exhibited a 47.1% relative reduction from baseline in LDL levels, compared with a 1.9% increase in the placebo group. This finding is consistent with the results of Stefanutti C, *et al*. who revealed that, LDL levels decreased by 46.8% after 24 months of evinacumab treatment in patients with HoFH.[14]

Evinacumab had been investigated on pediatric patients. [15 - 17] A case study HTG therapy with evinacumabin a 10-year-old boy showed that the drug was well tolerated and lower TG levels from 1,341 to 154 mg/dL within 24 h. [15] These studies have shown that evinacumab was effective in reducing TG and LDL levels in patients with HTG/or hypercholesterolemia and may prevent atherosclerosis development. Furthermore, a study demonstrated that the evinacumab doses utilized for the Caucasian population were similarly suitable for Japanese patients. [18]

Antisense oligonucleotide (ASO) therapy

Vupanorsen, also known as ANGPTL3-LRx, is a second-generation ligand-conjugated ASO that targets ANGPTL3 mRNA coding sequence in liver cells, ultimately inactivating its translation into ANGPTL3 protein. ASOs are relatively small molecules of 15 - 20 nucleotides in length that may accurately connect with corresponding mRNA sequences by RNA breakage or blocking. The mechanism of action and summary of the studies of vupanorsen are shown in **Figure 4 and Table 2,** respectively.

Vupanorsen dramatically lowered plasma ANGPTL3, TG and LDL levels, and the extent of the decline was dependent on the dose and frequency of injections. In phase 2 double-blind study, patients (n =105) with fasting TG levels 150 mg/dL were administered with 40 or 80 mg of vupanorsen SC every 4 weeks (Q4W) or 20 mg every week (QW) for 6 months. At the sixth months, the primary effectiveness outcome was the percentage decrease in fasting TG levels from baseline. TG level reductions of 36.0%, 53.0%, and 47.0%, and ANGPTL3 level reductions of 41.0%, 59.0%, and 56.0% were observed in the 40 mg Q4W, 80 mg Q4W, and 20 mg QW groups, respectively, compared with a 16.0% decrease in TG

Table 2. Results of the studies of vupanorsen.

Study	Design	Intervention	Results
Bergmark BA, *et al.*[20]	Double-blind, two hundred eighty-six subjects (triglycerides 150 to 500 mg/dL) were randomized: 44 to placebo and 242 to vupanorsen.	vupanorsen dose regimens (80, 120, or 160 mg SC every 4 weeks, or 60, 80, 120, or 160 mg SC every 2 weeks) for 24 weeks	There were dose-dependent reductions in triglycerides that ranged from 41.3% to 56.8%. The effect on LDL was 7.9% - 16.0%.
Gaudet D, *et al.*[19]	Double-blind, placebo-controlled, dose-ranging, Phase 2 study. Patients (n = 105) with fasting triglycerides >150 mg/dL.	Treated for 6 months with 40 or 80 mg every 4 weeks (Q4W), or 20 mg every week (QW) of vupanorsen, or placebogiven subcutaneo-usly.	Significant reductions in triglycerides of 36.0%, 53.0%, 47.0%, were observed in the 40 mg Q4W, 80 mg Q4W, and 20 mg QW groups, respectively, compared with 16.0% reduction in triglyce-rides in placebo.
Foss-Freitas MC, *et al.*[21]	Four patients with familial partial lipodystrophy (FPLD) (two with pathogenic variants in LMNA gene, and two with no causative genetic variant), hypertriglyce-ridemia (≥ 500 mg/dL), were included.	vupanorsen subcutaneously at a dose of 20 mg weekly for 26 weeks.	Treatment resulted in reduction in triglyce-rides by 59.9 %.

and an 8.0% increase in ANGPTL3 levels in the placebo group. The most prevalent adverse events were those at the injection site, which were not related to clinically significant changes in platelet counts.[19]

Moreover, a recent study of 286 patients with TG levels of 150-500 mg/dL on statin therapy showed that 24 weeks of vupanorsen treatment (80, 120, or 160 mg (SC) every 4 weeks, or 60, 80, 120, or 160 mg SC every 2 weeks) substantially reductions TG levels by 44.0%, 41.3%, 45.9%, 43.8%, 50.5%, 50.7% and 56.8% respectively. The effect on LDL levels was ranged from 7.9% - 16.0%.[20] This finding is consistent with the result of Foss-Freitas MC, *et al*. who revealed that TG levels decreased by 59.9% in patients with HTG treated with vupanorsen 20 mg weekly for 26 weeks.[21] These findings demonstrated that vupanorsen offered a possible method for lowering TG, and LDL levels and cardiovascular risk.

Vaccine

Previous studies have demonstrated that vaccines based on virus-like particles (VLPs) can be utilized as platforms to produce potent antibody responses against self-proteins. A mouse study produced VLP-based vaccines that target the ANGPTL3 LPL binding domains. A promising alternative to existing ANGPTL3-inhibiting drugs is ANGPTL3 targeting by active immunization, which rapidly decreases the circulating TG levels and increases plasma LPL activity.[22]

Recently, three epitopes (E1-E3) were designed for use in the development of a peptide vaccine targeting ANGPTL3 and the estimated effects of each on dyslipidemia mice. Vaccination with the E3 (^{32}EPKSRFAMLD^{41}) peptide significantly reduced the circulating levels of TG and LDL. Moreover, E3 vaccination does not induce cytotoxicity in mice. Interestingly, the effect of E3 vaccination on dyslipidemia attenuated the development of atherosclerosis in B6.KOR/StmSlc-*Apoe*^{shl} mice fed a high-cholesterol diet, which represents a model of severe familial hypercholesterolemia (FH). This ANGPTL3 vaccine improved dyslipidemia and atherosclerosis in FH model mice.[23] The mechanism of action of the ANGPTL3 vaccine is shown in **Figure 5.**

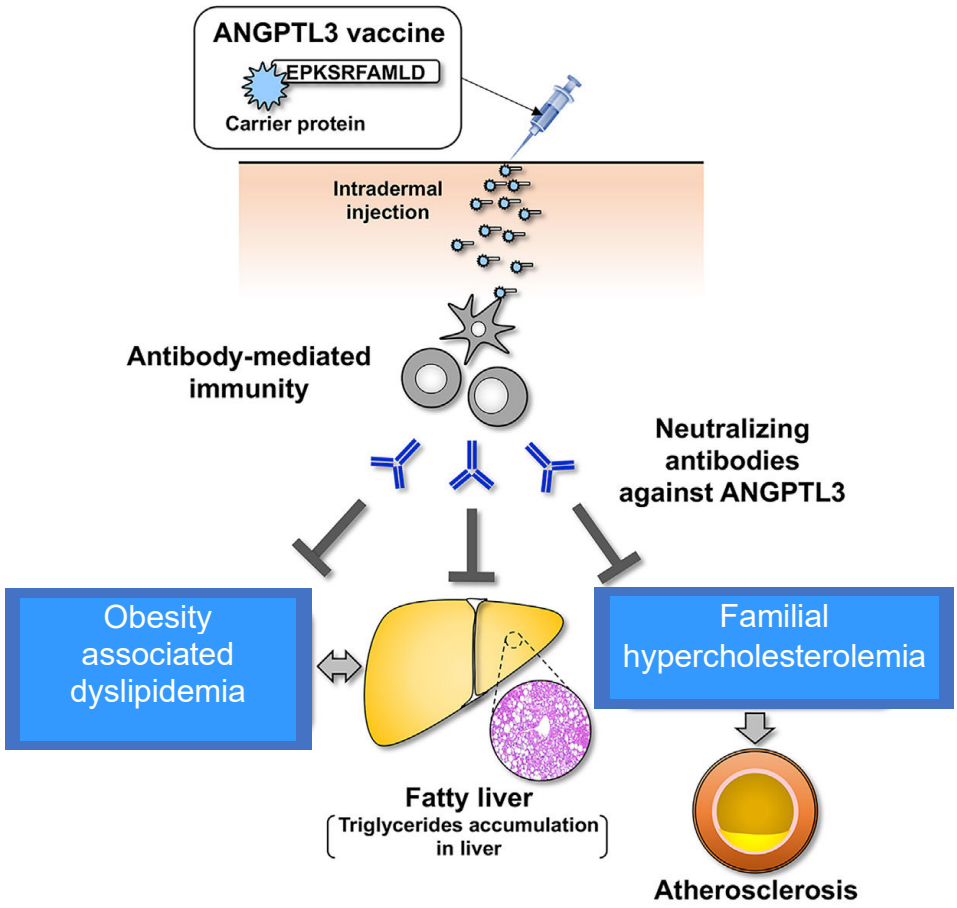

Figure 5. Mechanism of action of ANGPTL3 vaccine.[23]

Conclusion

Deep phenotyping in families, gene sequencing in the population, and biomarker analysis in cases and controls showed that ANGPTL3 deficiency is associated with lower TG and LDL levels. Therefore, ANGPTL3 is a good target for a reduced risk of atherosclerosis. ANGPTL3 inhibition is a promising new strategy for treating atherogenic dyslipidemia. However, the global implementation of treatment with anti-ANGPTL3 antibodies or ASO is limited because of to the economic burden of prolonged therapy required for these targeted agents. Thus, more cost-effective therapeutic options are need.

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Conflicts of interest statement

All authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors disclose any conflict of interest.

Data sharing statement

This review is based on the references cited. All data generated or analyzed in this study are included in this published article and the citations herein. Further details, opinions, and interpretation are available from the corresponding author on reasonable request.

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