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Evinacumab — an ANGPTL3 inhibitor; a new drug in the treatment of lipid disorders Review on the literature and clinical studies

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Abstract

Angiopoietin-like proteins (ANGPTL) are a family of several proteins, of which ANGPTL3, 4 and 8 are involved in lipid metabolism. These proteins, discovered relatively recently, regulate the availability of triglycerides for the heart, skeletal muscles and white and brown adipose tissue depending on the nutritional status of the body, thus contributing to the maintenance of energy homeostasis. *ANGPTL3, 4* and *8* gene mutations are associated with a significant reduction in plasma lipid levels, which translates to a reduction in the risk of ischaemic heart disease and diabetes type 2. It was shown that blood levels of ANGPTL3, 4, 5 and 8 may change in various disease states, such as obesity or diabetes type 2, and thus may constitute biomarkers of the cardiovascular risk. Evinacumab, being a fully humanized anti-ANGPTL3 antibody, February, 11th, 2021, as Evkeeza® preparation, has been registered by the US Food and Drug Administration for the treatment of homozygous familial hypercholesterolaemia. In clinical trials, evinacumab was characterized by a high lipid-lowering efficacy in patients with homozygous and heterozygous familial hypercholesterolaemia, as well as treatment-resistant hypercholesterolaemia and hypertriglyceridaemia. Another drug that reduces ANGPTL3 activity are antisense oligonucleotides targeting *Angptl3* mRNA (ANGPTL3 ASO) which were also characterized by lipid lowering properties in clinical trials.

Key words: ANGPTL3, ANGPTL4, ANGPTL8, evinacumab, ANGPTL3 ASO, treatment of lipid disorders

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Characteristics and role of angiopoetin-like proteins in the lipid and carbohydrate metabolism

Angiopoetin-like proteins (ANGPTL) are a group of proteins currently encompassing compounds ANGPTL1 through ANGPTL8 which belong to the family of vascular endothelial growth factor (VEGF). From the cardiovascular perspective, the important compounds are ANGPTL3, ANGPTL4 and ANGPTL8, as they are involved in the metabolism of triglyceride-rich lipoproteins [1]. These proteins were discovered in 1999, 2000, and 2012, respectively, and are characterized by a similar structure, with a fibrinogen-like C-terminal domain. The exception is ANGPTL8 which does not include this domain in its structure. The main sources of these proteins are the liver for ANGPTL3, the liver, adipose tissue, skeletal muscle, intestines, heart, and brain for ANGPTL4, and the liver and adipose tissue for ANGPTL8 [2, 3].

These proteins form a system that controls the availability of triglycerides depending on the current body nutrition status, temperature, and physical activity. Following a meal, triglycerides are stored in the white adipose tissue. During fasting, they become an energy substrate for the heart, skeletal muscle, and brown adipose tissue. Triglyceride availability is regulated by lipoprotein lipase (LPL).

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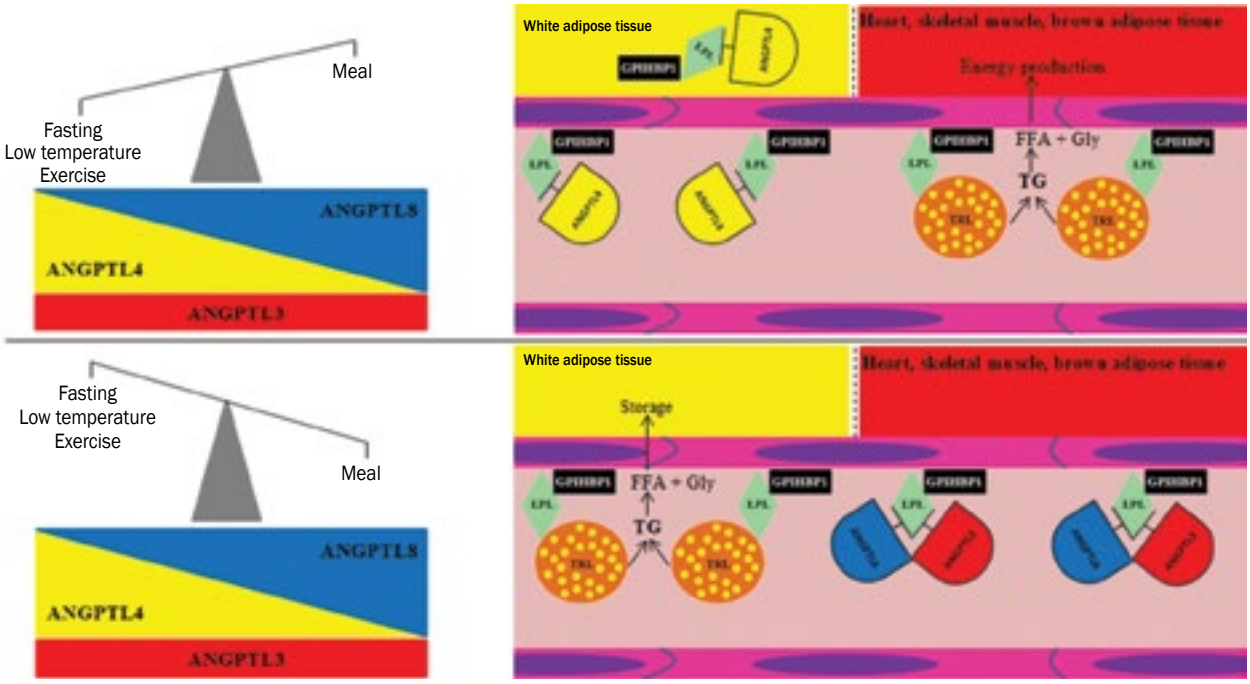

Figure 1. Regulation of triglyceride metabolism by ANGPTL3, 4 and 8 (based on [1–5]); ANGPTL3, 4 and 8 — angiopoetin-like protein 3, 4 and 8; LPL — lipoprotein lipase; GPIHBP1 — glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1; FFA — free fatty acids; Gly — glycerol; TG — triglycerides; TRL — triglyceride-rich lipoproteins

Following a meal, LPL activity increases in the white adipose tissue and decreases in the heart, skeletal muscle and brown adipose tissue, while during fasting, LPL activity increases in the heart, skeletal muscle and brown adipose tissue, and decreases in the white adipose tissue [4]. Stimulation of LPL depends on ANGPTL3, 4 and 8. It was shown that ANGPTL3, ANGPTL4 and ANGPTL8 reduce LDL activity by changing its conformation from a homodimeric one (biologically active) to a monomeric one (biologically inactive), which is associated with a reduced LDL affinity to its stabilizing factor, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1) [1]. In addition, ANGPTL3 reduces the activity of endothelial lipase (EL) [5] In the heart, skeletal muscle and brown adipose tissue, postprandial LDL activity is reduced by ANGPTL3 and ANGPTL8 (ANGPTL8 expression is increased after a meal, while ANGPTL3 expression is not dependent on the nutrition status) that form a heterodimer (ANGPTL8 is an activator of ANGPTL3). In contrast, LPL activity in the white adipose tissue during fasting is decreased by ANGPTL4 (intracellularly and extracellularly) (Figure 1) [1–5].

Factors stimulating ANGPTL3, 4 and 8 depending on the nutrition status have not been clearly identified. Postulated factors include a role of insulin and leptin in the regulation of *ANGPTL3* expression, of glycocorticosteroids in the regulation of *ANGPTL4* expression, and of sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate-responsive element-binding protein (ChREBP) in the regulation of *Angptl8* expression [2, 4].

Thus, ANGPTL3, 4 and 8 play a major role in the lipoprotein metabolism by regulating triglyceride hydrolysis depending on the body nutrition status. This mechanism is related to posttranslational LPL modification by these proteins.

These proteins, particularly ANGPTL4, also play a role in carbohydrate metabolism. Glucose tolerance improvement and an increase in blood insulin level were shown in *Angptl4* knockout (*Angptl4*$^{-/-}$) mice [6]. These effects were likely related to the fact that an increase in LPL activity has a beneficial effect on the body energy homeostasis [7]. The role of ANGPTL3 in the carbohydrate metabolism is unclear and requires further studies [2]. A beneficial effect of ANGPTL8 on pancreatic beta cell proliferation was initially suggested, and the protein was named betatrophin but further studies did not confirm these observations [2, 8]. It should also be noted that these proteins also exert other metabolic effects that have often not been well characterized [9].

ANGPTL3, ANGPTL4 and ANGPTL8 and cardiovascular risk

The interest in ANGPTL3, 4 and 8, in addition to their effect on metabolism, is related to the fact that mutations of genes coding for these proteins lead to significant

alterations of the lipid profile with resultant effects on the cardiovascular risk, and that blood levels of these proteins change in various diseases.

In the study by Sitiziel et al. [10], the effect of ANGPTL3 deficiency on the coronary atherosclerosis burden and the risk of ischaemic heart disease was evaluated. In addition, this study evaluated the relationship between plasma ANGPTL3 level and the risk of myocardial infarction. In individuals with total ANGPTL3 deficiency, coronary atherosclerotic plaques were absent. The prevalence of heterozygous loss of function (LOF) *Angptl3* gene mutation was 1:309. In heterozygous LOF *Angptl3* gene mutation carriers, plasma total cholesterol, triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were reduced by 11%, 17%, 12%, and 5%, respectively, and these changes translated to a 34% lower risk of ischaemic heart disease. It was found that plasma ANGPTL3 level was related to the risk of myocardial infarction. Compared to individuals with higher plasma ANGPTL3 levels, those with plasma ANGPTL3 levels of 272–378 ng/mL and 18––271 ng/mL were characterized by a 21% and 29% lower risk of myocardial infarction, respectively [10].

A similar study was performed by Dewey et al. [11]. In the study by these authors, *ANGPTL3* gene exons were sequenced in nearly 60,000 participants of the DiscovEHR Study. This was followed by an analysis of the relation between the presence of normal *ANGPTL3* gene or LOF mutations of this gene and serum lipid levels [11].

It was found that the LOF *ANGPTL3* gene mutation carriers were characterized by lower levels of the four major plasma lipid fractions, which translated to a 39% lower risk of ischaemic heart disease in these individuals [11].

In another study in more than 42,000 participants of the DiscovEHR Study, Dewey et al. [12] evaluated the relation between inactivating *ANGPTL4* gene mutations and plasma lipid levels and the risk of ischaemic heart disease. It was shown that inactivation of the *ANGPTL4* gene was most commonly caused by a heterozygous E40K mutation and resulted in a reduction in plasma total cholesterol, LDL, and triglyceride levels along with an increase in plasma HDL level [12].

Individuals with the E40K *ANGPTL4* gene mutation (either heterozygous or homozygous) were characterized by a 19% lower risk of ischaemic heart disease. Other inactivating *ANGPTL4* gene mutations led to insignificant reductions of the ischaemic heart disease risk [12]. Similar results were obtained by Sitiziel et al. [13] in a study in nearly 194,000 individuals. These authors showed that E40K *ANGPTL4* gene mutation carriers had a 35% lower plasma triglyceride levels and a 53% lower risk of ischaemic heart disease [13].

In an interesting study in more than 310,000 individuals, Klarin et al. [14] evaluated the effect of LOF *ANGPTL4* gene mutations on the risk of ischaemic heart disease and diabetes type 2. It was shown that the E40K *ANGPTL4* gene mutation was associated by a 16% lower risk of ischaemic heart disease and a 12% lower risk of diabetes type 2 [14]. Gusarova et al. [15] in a study in more than 58,000 participants of the DiscovEHR Study also evaluated the effect of the E40K *ANGPTL4* gene mutation on the risk of diabetes type 2. Interestingly, this study also showed that the risk of diabetes type 2 was 12% lower in the E40K *ANGPTL4* gene mutation carriers. The authors concluded that this beneficial effect of the E40K *ANGPTL4* gene mutation was due to lower fasting blood glucose levels and higher insulin sensitivity in the individuals carrying this mutation [15].

The effect of LOF *ANGPTL8* gene mutations on the cardiovascular risk was evaluated by Peloso et al. in a study in more than 56,000 individuals. The LOF *ANGPTL8* gene mutation carriers were shown to have a 10 mg/dL lower plasma HDL level, and a 15% lower plasma triglyceride level. The effect of this mutation on plasma LDL level was not significant. Of interest, LOF *ANGPTL8* gene mutation carriers were not found to have a lower risk of ischaemic heart disease [16].

Use of ANGPTL3, 4 and 8 as potential cardiovascular risk biomarkers was evaluated by Morinaga et al. in a cross-sectional study in 988 Japanese individuals. It was shown that serum ANGPTL3 level was relatively high in study participants with liver dysfunction and inflammation, while serum ANGPTL4 level was significantly elevated in case of impaired carbohydrate metabolism and liver failure but lower in inflammation. Finally, elevated serum ANGPTL8 level was seen in patients with obesity, impaired carbohydrate metabolism, and dyslipidemia. In particular, elevated serum ANGPTL8 level showed a positive association with plasma triglyceride and LDL levels and a negative association with plasma HDL level. Thus, serum ANGPTL3, 4 and 8 levels may be helpful in the evaluation of cardiovascular risk [17].

In turn, Alghanim et al. [18] indicated a role for ANGPTL5 in the evaluation of cardiovascular risk in 2019. The study included 204 individuals, including 66% with obesity and/or diabetes type 2. Plasma ANGPTL5 level was found to be elevated in individuals with obesity and/or diabetes type 2. In addition, positive associations were found between plasma ANGPTL5 level and fasting blood glucose level, haemoglobin A_{1c} (HbA_{1c}) level, plasma triglyceride level, and insulin resistance as evaluated by the homeostatic model assessment — insulin resistance (HOMA-IR). From a clinical perspective, it should be noted that this study showed a gradual increase in plasma ANGPTL5 level in prediabetes [18].

In a recent study by Hammad et al. [19] in 431 adolescents, with more than 50% of them with an increased body weight, changes in ANGPTL5 level in relation to body weight were analysed. In addition, plasma high-sensitivity C-reactive protein (hsCRP) and oxidized LDL (ox-LDL) levels

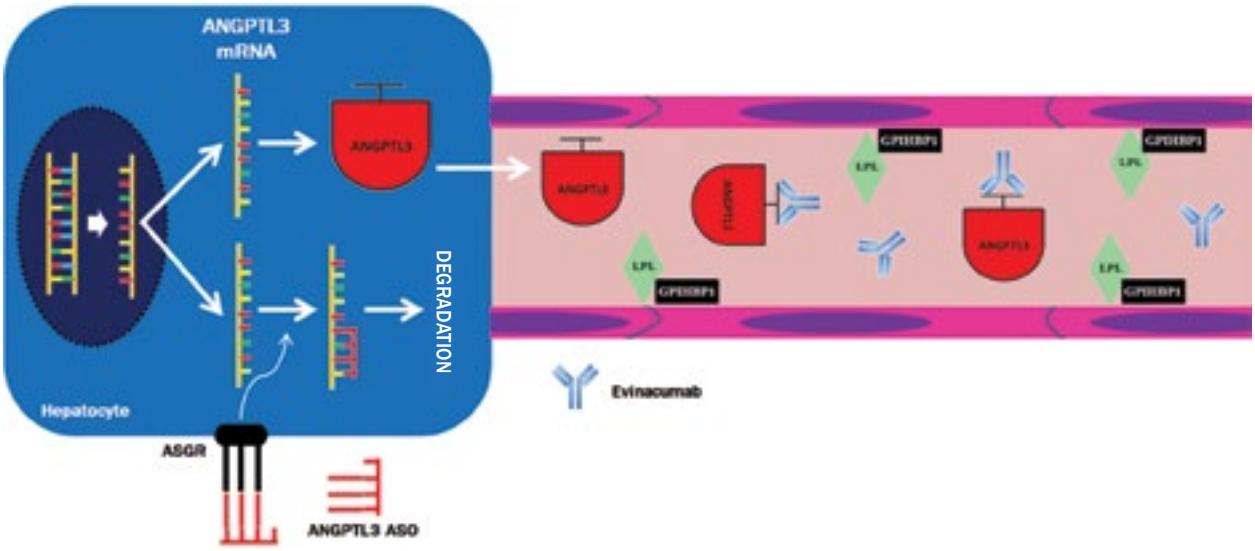

Figure 2. Mechanism of action of evinacumab and antisense oligonucleotides targeting *Angptl3* mRNA (ANGPTL3-LRx) (based on [28]); ASGR — asialoglycoprotein receptor; ANGPTL3 — angiopoetin-like protein 3; mRNA — messenger RNA; ANGPTL3 ASO — antisense oligonucleotides targeting ANGPTL3 mRNA; LPL — lipoprotein lipase; GPIHBP1 — glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1

were measured. ANGPTL5 level was found to be significantly increased in obese adolescents but it did not differ between normal body weight and overweight study participants [19].

In addition, plasma ANGPTL5 level showed a positive correlation with plasma hsCRP and ox-LDL levels [19].

Taking into account the results of other studies that showed that plasma ANGPTL3 and ANGPTL8 levels did not differ between normal body weight and obese adolescents [19–21], the study authors suggested that plasma ANGPTL5 level may be a specific biomarker of the cardiovascular risk in this age group [19].

Thus, it seems that ANGPTL5 secreted by the heart may play a yet unelucidated role in lipid metabolism [3].

In summary, LOF *Angptl3, 4* and *8* gene mutations lead to lower plasma lipid levels. LOF *Angptl3 and Angptl4* gene mutations are also associated with a significantly lower risk of ischaemic heart disease and diabetes type 2. In addition, changes in ANGPTL3, 4 and 8 levels may be biomarkers of the cardiovascular risk. ANGPTL5 also seems to be an interesting marker of the risk of carbohydrate metabolism disturbances and the cardiovascular risk (particularly in adolescents).

ANGPTL3, 4 and 8 as targets for drug therapy of cardiovascular disease

The interest in a major role of ANGPTL3, 4 and 8 in lipid metabolism led to the development of compounds that would decrease the activity of these proteins. In experimental studies, use of a fully humanized antibody against ANGPTL4 (REGN1001) significantly reduced plasma lipid levels and improved carbohydrate metabolism but was associated with mesenteric lymph node inflammation [12, 23–25], and use of a fully humanized antibody against ANGPTL8 (REGN3776) led to a decrease in plasma triglyceride level and body weight reduction [26]. However, as shown earlier, the lipid-lowering effect of reduced ANGPTL8 activity did not translate to an effect on the cardiovascular risk in humans [16].

Results of the clinical studies are available that evaluated a fully humanized antibody against ANGPTL3 (evinacumab) and antisense oligonucleotides targeting *Angptl3* mRNA (ANGPTL3 ASO), administered in healthy volunteers and patients with lipid disorders.

Evinacumab

Evinacumab (RENG1500) is a fully humanized monoclonal antibody IgG4 against ANGPTL3 developed by Regeneron Pharmaceuticals, administered subcutaneously or intravenously [27]. Evinacumab, being a fully humanized anti-ANGPTL3 antibody, February, 11th, 2021, as Evkeeza® preparation, has been registered by the US Food and Drug Administration (FDA) for the treatment of homozygous familial hypercholesterolaemia (HoHF).

The mechanism of action of evinacumab involves reducing the activity of circulating ANGPTL3 by forming a complex with its molecule (Figure 2) [28].

Thus, indirect effects of the action of evinacumab include increased LPL and EL activity, reduced release of very low-density lipoproteins (VLDL), increased clearance of triglyceride-rich lipoproteins, and reduced lipolysis in the adipose tissue [29].

The first randomized, double-blind, placebo-controlled trial to evaluate the safety, activity profile and pharmacokinetics of evinacumab was conducted by Dewey et al. This study included 83 healthy subjects with plasma triglyceride level of 150–450 mg/dL and plasma LDL level of ≥ 100 mg/dL. The study subjects were randomized to groups that received evinacumab intravenously (5, 10 or 20 mg/kg body weight), evinacumab subcutaneously (75, 150 or 250 mg) or placebo. The most common adverse effect was headache (in 11% of the study subjects treated with evinacumab). There were no instances of evinacumab treatment withdrawal due to adverse effects. The maximum reduction in plasma triglyceride, LDL, and HDL levels, by 76% (day 4), 23.2% (day 15) and 18.4% (day 15), respectively, was observed in the group receiving evinacumab intravenously at the dose of 20 mg/kg body weight [11].

The safety, tolerance, pharmacokinetics, and potency of the lipid-lowering effect of evinacumab administered subcutaneously or intravenously were also evaluated in a randomized, double-blind, placebo controlled trial by Harada-Shiba et al. [30] in 96 healthy individuals with plasma LDL level of ≥2 .6 to < 4.1 mmol/L (≥ 100 to < 160 mg/dL). The study subjects were divided into 4 cohorts: I — 300 mg of evinacumab subcutaneously in a single dose; II — 5 mg/kg body weight of evinacumab intravenously, two doses 4 weeks apart; III — 15 mg/kg body weight of evinacumab intravenously, two doses 4 weeks apart; and IV — 300 mg of evinacumab subcutaneously once a week for 8 weeks. Each cohort included 24 individuals (12 Japanese and 12 Caucasians) who were randomized (3:1) to evinacumab or placebo. The duration of follow-up was 24 weeks. The safety profile of evinacumab (administered intravenously or subcutaneously) in both ethnic groups was shown to be comparable to placebo, without serious or severe adverse events. The pharmacokinetic profiles of evinacumab (administered intravenously or subcutaneously) were comparable between the study groups [30].

A dose-related decrease in plasma LDL, triglyceride, non-HDL, HDL, total cholesterol, apolipoprotein (apo) B, apo A-I, apo C-III, and lipoprotein(a) [Lp(a)] level was found. Administration of two evinacumab doses of 15 mg/kg body weight intravenously, 4 weeks apart, was characterized by the highest potency of the lipid-lowering effect (reduction in plasma LDL, triglyceride, non-HDL, HDL, total cholesterol, apo B, apo A-I, apo C-III, and Lp(a) level at 8 weeks by 40%, 63%, 44%, 24%, 41%, 30%, 41%, 78%, and 35%, respectively) [30].

Evinacumab in the treatment of homozygous familial hypercholesterolemia

The lipid-lowering efficacy of evinacumab in 9 patients with HoHF was evaluated by Gaudet et al. [31] Despite aggressive treatment used in the study subjects before recruitment to the trial [statins, ezetimibe, lomitapide, proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors], their mean plasma LDL level was 376 ± 240.9 mg/dL. The study subjects received evinacumab subcutaneously in a single 250 mg dose, followed by an intravenous dose of 15 mg/kg body weight 2 weeks later. No serious adverse effects were observed during the 4-week follow-up. The mean reduction in triglyceride, LDL, HDL, non-HDL, and apo B level at 4 weeks was 47%, 49%, 36%, 49%, and 46%, respectively [31]. Of interest, an analysis of LDL receptor activity in lymphocytes harvested from these patients with HoHF showed that evinacumab reduced plasma LDL level via an LDL-receptor independent mechanism [32].

In the most recent double-blind placebo-controlled phase III trial (ELIPSE-HoHF Study), Raal et al. evaluated the therapeutic efficacy of evinacumab in 65 patients with HoHF. The study subjects were administered evinacumab 15 mg/kg body weight intravenously every 4 weeks or placebo. The mean baseline plasma LDL (Figure 3), level was 255 mg/dL despite intensive lipid-lowering treatment. At 24 weeks, plasma LDL, total cholesterol, triglycerides, non-HDL, apo B, apo C-III, and Lp(a) level was noted to be significantly reduced by 47%, 47%, 55%, 50%, 41%, 84%, and 6%, respectively [33].

Of note, a reduction in plasma LDL by at least 50% was observed in 56% of the study subjects treated with evinacumab. At 24 weeks of evinacumab treatment, 28% of the patients had plasma LDL level below 70 mg/dL. The lipid-lowering efficacy of evinacumab was independent from the type of LDL receptor gene mutation (*non/null* or *null/null*). No serious adverse events were noted during evinacumab treatment [33].

Evinacumab in the treatment of heterozygous familial hypercholesterolaemia or treatment-resistant hypercholesterolaemia

In a recently published double-blind, placebo-controlled phase II trial, Rosenson et al. [34] evaluated the lipid-lowering efficacy of evinacumab in patients with heterozygous familial hypercholesterolaemia (HeHF) or treatment-resistant hypercholesterolaemia. The study included 272 patients, including 202 with HeHF. At baseline, all study subjects were on intensive lipid-lowering therapy, and the mean baseline plasma LDL level was 144–150 mg/dL. The patients were randomized to evinacumab intravenously (15 mg/kg bw every 4 weeks or 5 mg/kg bw every 4 weeks or placebo) or subcutaneously (450 mg once a week or 300 mg once a week or 300 mg once every two weeks or placebo). The duration of follow-up was 16 weeks. During the study, the most common adverse effects in the subcutaneous evinacumab group included headache, erythema at the injection site,

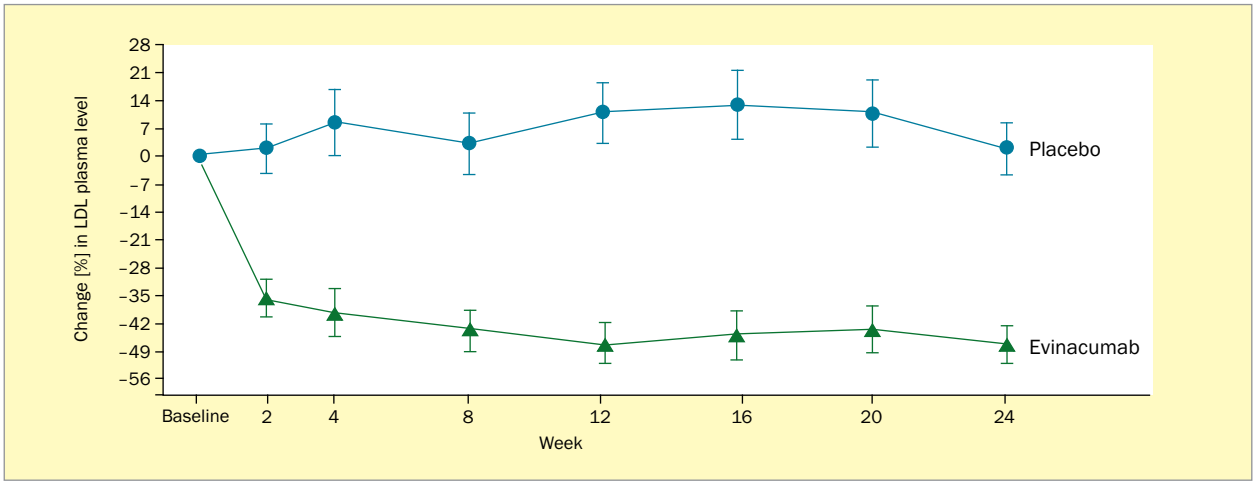

Figure 3. Change in plasma low-density lipoprotein (LDL) cholesterol levels in patients receiving placebo or intravenous evinacumab 15 mg/kg every 4 weeks (based on [33])

nausea, sore throat, nasopharyngitis, back pain, urinary tract infection, and constipation, while the most common adverse effects in the intravenous subcutaneous evinacumab group were: blood pressure elevation, nasopharyngitis, fatigue, muscle pain, and headache. A significant reduction in plasma LDL level was shown (Figure 4) [34].

Despite previous intensive lipid-lowering therapy, use of evinacumab in patients with HeHF and treatment-resistant hypercholesterolaemia lead to plasma LDL reduction by another 50% [34].

Evinacumab in the treatment of hypertriglyceridaemia

Ahmad et al. conducted two phase I clinical trials to evaluate the safety and efficacy of evinacumab in the treatment of hypertriglyceridaemia. The studies included individuals with plasma triglyceride level > 150 to ≤ 450 mg/dL and plasma LDL level ≥ 100 mg/dL. The study with single increasing evinacumab doses (subcutaneous: 75, 150 or 250 mg; intravenous: 5, 10 or 20 mg/kg bw, or placebo) included 83 patients who were followed up for 126 days. The study with multiple increasing evinacumab doses (subcutaneous: 150, 300 or 450 mg once a week or 300/400 mg every 2 weeks; intravenous: 20 mg/kg body weight every 4 weeks for 8 weeks) included 56 patients who were followed up for 6 months. Evinacumab was shown to be well tolerated. A significant reduction in plasma triglyceride level was noted (Figure 5) [35].

The maximum reduction in plasma triglyceride level with single increasing evinacumab doses was observed for the dose of 10 mg/kg body weight intravenously on Day 3 (reduction by 76.9%), and with multiple increasing evinacumab doses for the dose of 20 mg/kg body weight intravenously every 4 weeks on Day 2 (reduction by 83.1%) [35].

It was found that use of evinacumab resulted in a plasma triglyceride level reduction comparable to that observed in individuals with LOF *ANGPTL3* gene mutation [35].

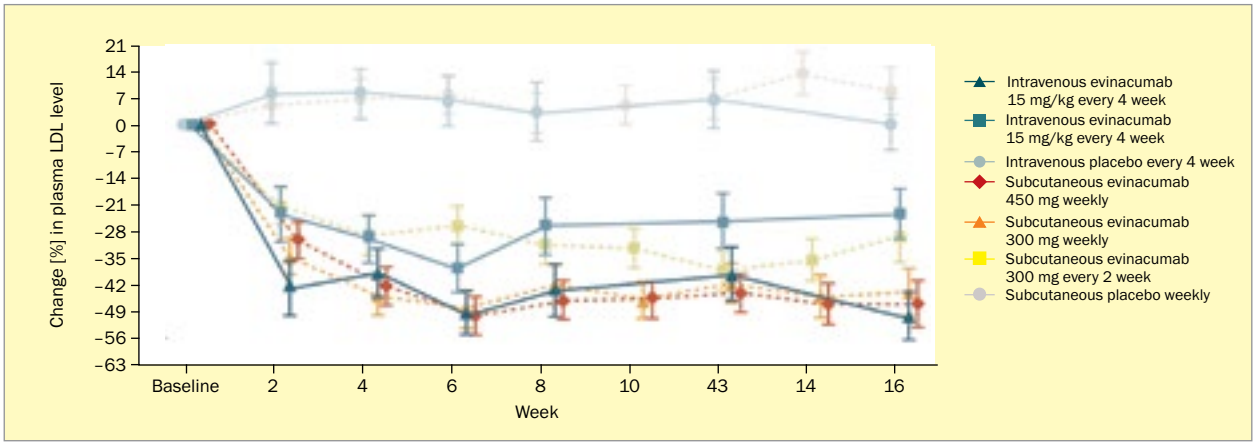

Figure 4. Changes in plasma low-density lipoprotein (LDL) level over 16 weeks of treatment (based on Rosenson et al. [34])

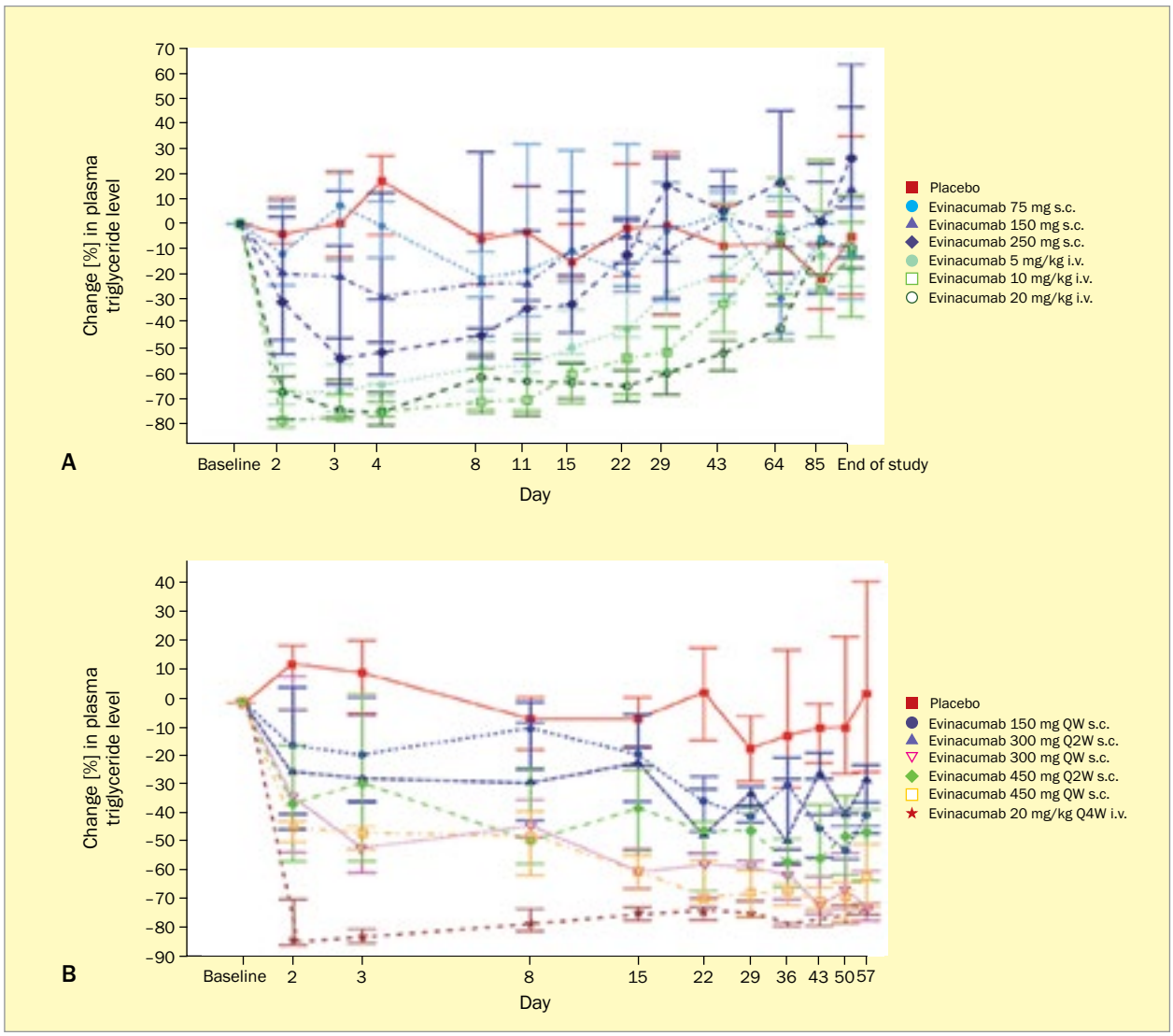

Figure 5. Changes in plasma triglyceride level with single (**A**) or multiple (**B**) increasing evinacumab doses (based on Ahmad et al. [35]); *s.c.* — subcutaneous; *i.v.* — intravenous; QW — weekly; Q2W — every 2 weeks

Currently, studies are underway that evaluate evinacumab treatment in patients with HoHF (NCT03409744, planned completion in 2022) and in children with HoHF (NCT04233918, planned completion in 2023). Another study has been completed that evaluated evinacumab treatment in patients with severe hypertriglyceridaemia and an increased risk of acute pancreatitis (NCT0345228) and a study evaluating the effect of evinacumab on lipid metabolism in adult patients with HoHF (NCT04722068).

Evkeeza®

As already mentioned, in February 2021 the FDA registered evinacumab known as Evkeeza® for the treatment of patients aged 12 years and older with HoHF. Recommended dose of the preparation is 15 mg/kg bw administered intravenously every 4 weeks. The drug infusion takes about 60 min, while the lowering LDL cholesterol levels can be determined after 2 weeks from application. For the most common activities side effects of the drug include rhinitis and throat (16%), flu-like illness (7%), dizziness (6%), nasal discharge (5%) and nausea (5%) [36]. Expense annual treatment with Evkeeza® is approx 450 USD.

ANGPTL3 ASO

As shown in Figure 2, ANGPTL3 ASO interacts with the asialoglycoprotein receptor (ASGR), resulting in degradation of ANGPTL3 mRNA in hepatocytes. The overall effect of ANGPTL3 ASO administration is thus a reduction of ANGPTL3 production in hepatocytes (Figure 2) [28].

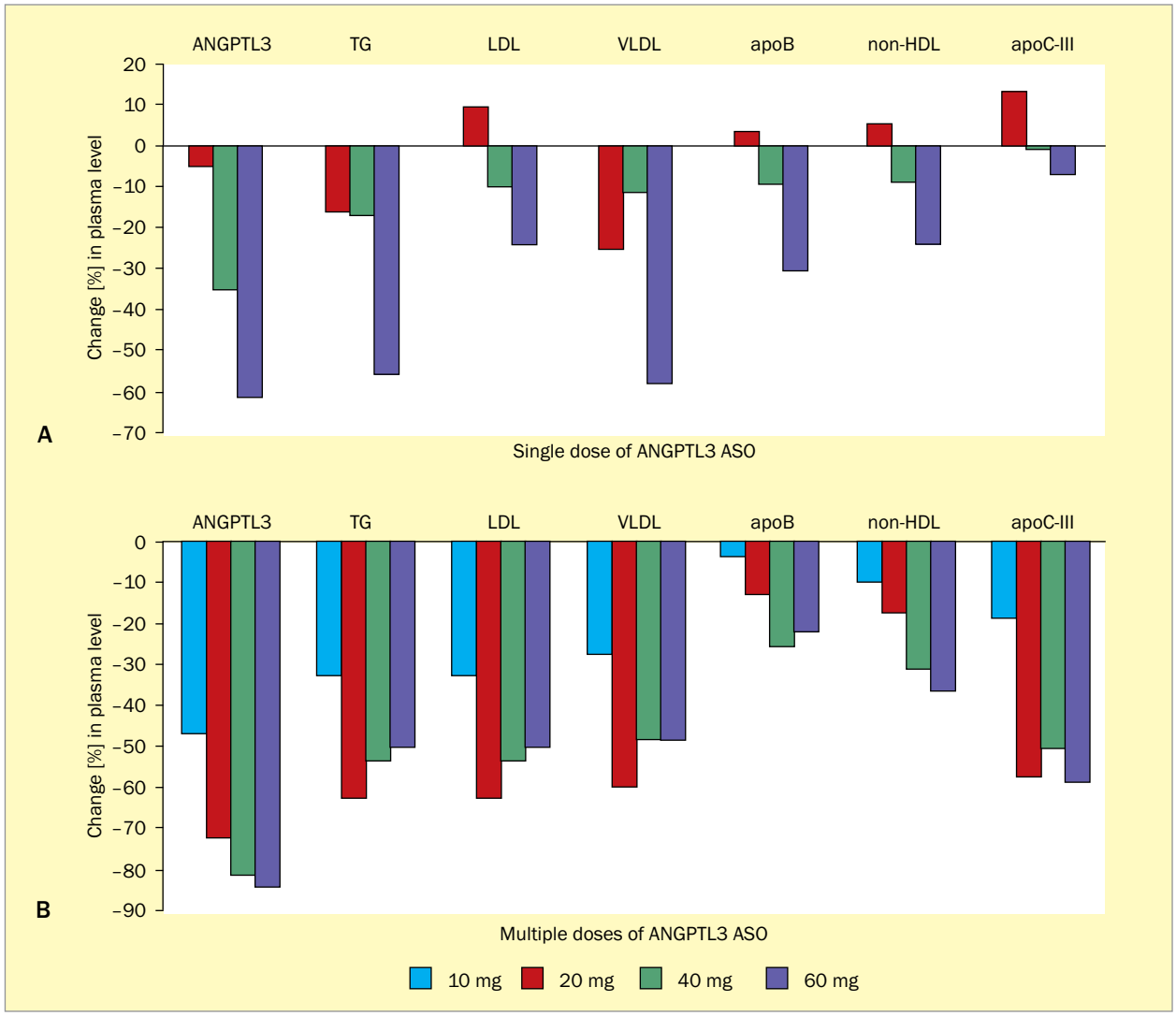

Figure 6. Changes in plasma angiopoetin-like protein 3 (ANGPTL3) and lipid levels during treatment with multiple (**A**) or single (**B**) ANGPTL3 ASO injections (based on Graham et al. [36]); TG — triglycerides; LDL — low-density lipoproteins; VLDL — very low-density lipoproteins; apoB — apolipoprotein B; HDL — high-density lipoproteins; apoC-III — apolipoprotein C-III

The safety, pharmacokinetics, and efficacy of ANGPTL3 ASO were evaluated by Graham et al. in 44 individuals with plasma triglyceride level of 90–150 mg/dL or > 150 mg/dL. The study subjects were randomized to subcutaneous injections of ANGPTL3 ASO or placebo in a single dose (20, 40 or 80 mg) or multiple doses (10, 20, 40 or 60 mg once a week for 6 weeks). No serious adverse events were reported during the study (most commonly reported adverse effects were dizziness and headache). A reduction in plasma ANGPTL3 and lipid levels was noted (Figure 6) [36].

Administration of ANGPTL3 ASO resulted in a reduction of the plasma level of atherogenic lipoproteins [36].

Studies have been completed that evaluated ANGPTL3 ASO (ISIS 703802) in the treatment of familial partial lipodystrophy (NCT03514420) and familial chylomicronaemia (NCT03360747) and in the treatment of patients with hypertriglyceridemia, type 2 diabetes and non-alcoholic fatty liver disease (NCT03371355).

Summary

Angiopoetin-like proteins do not currently have an established therapeutic role in the management of hypercholesterolaemia, diabetes, and obesity, and we are still lacking complete pathophysiological data that would allow a clear definition of their role in the cardiovascular disease [38]. Paradoxically, however, a rapid and satisfactory clinical trial program of the new monoclonal antibody (evinacumab) developed by a leading pharmaceutical company Regeneron,

with the availability of this drug on the market from February 2021, allow us to summarize the current knowledge about these proteins in the following way:

- ANGPTL3, 4 and 8 seem to play a major role in lipid metabolism by regulating triglyceride availability for the heart, skeletal muscle, and white and brown adipose tissue in relation to the body nutrition status;
- changes in plasma ANGPTL3, 4, 5 and 8 levels may be cardiovascular risk markers;
- evinacumab, a fully humanized antibody against ANGPTL3, has been characterized by a good tolerance and potent lipid-lowering properties in the studies in patients with HoHF, HeHF, treatment-resistant hypercholesterolaemia and hypertriglyceridaemia and will be soon available clinically;
- evinacumab in the form of Evkeeza® stayed in February 2021 registered by the FDA for treatment HoHF in people aged 12 years and older;
- more studies on evinacumab and further drugs of this class are required, in particular regarding head-to-head comparisons and combination therapy with PCSK9 inhibitors;
- drugs of this class may also represent the long-awaited advance in the management of hypertriglyceridemia as add-ons to omega-3 fatty acids and fibrates.

Conflict of interests

The authors declare no conflict of interests.

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