International Journal of Clinical and Translational Medicine
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Mini- Review

Apolipoprotein C-III and Pathophysiology of Severe Hypertriglyceridemia: A New Frontier in Therapeutic Intervention

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How To Cite: Duell, PB. Apolipoprotein C-III and Pathophysiology of Severe Hypertriglyceridemia: A New Frontier in Therapeutic Intervention. *International Journal of Clinical and Translational Medicine* **2025**, *1*(*2*), 1. https://doi.org/10.53941/ijctm.2025.100008.

Received: 11 March 2025
Accepted: 21 March 2025
Published: 8 April 2025

Abstract: Apolipoprotein C-III (apo C-III) is an important regulator of metabolism of triglyceride-rich lipoproteins that include hepatically-derived very low-density lipoproteins, intestinally derived chylomicrons, and remnant lipoproteins. Apo C-III is carried on triglyceride-rich lipoproteins, but exchanges bidirectionally with high-density lipoprotein particles. Apo C-III inhibits lipoprotein lipase (LPL), a key mediator of clearance of triglycerides from plasma, thereby contributing to hypertriglyceridemia. Apo C-III is also involved in hepatic VLDL synthesis and secretion, interferes with apo E-mediated clearance of triglyceride-rich lipoproteins, has proinflammatory properties, and has a causative role in development of atherosclerotic cardiovascular disease. Familial chylomicronemia syndrome (FCS) is a rare recessive condition caused by defects in LPL, or four associated proteins, and is associated with severe hypertriglyceridemia and recurrent pancreatitis. Standard triglyceride-lowering interventions lack efficacy in patients with FCS, so there has been a quest to develop efficacious and safe medications for treatment of FCS. In December 2024, olezarsen, an antisense oligonucleotide medication targeting apo C-III, was FDA approved for treatment of patients with FCS. It substantially lowered levels of apo C-III and triglycerides in plasma and reduced the incidence of pancreatitis by 88%. Plozasiran, an experimental small interfering RNA compound targeting apo C-III that may be approved in late 2025, also substantially lowered levels of apo C-III and triglycerides in plasma and reduced pancreatitis risk by 83%. The availability of olezarsen, and possible availability of plozasiran later this year, has ushered in a new era of highly efficacious treatments for FCS that can prevent pancreatitis and improve quality of life.

Keywords: apolipoprotein C-III; apo C-III; hypertriglyceridemia; familial chylomicronemia syndrome (FCS); olezarsen; plozasiran

1. Introduction

Apolipoprotein C-III (apo C-III) is an important regulator of triglyceride metabolism and modulator of atherosclerotic cardiovascular (ASCVD) risk that was first discovered in 1969 by Brown and colleagues. Initial studies showed that apo C-III attenuated clearance of triglyceride-rich lipoproteins from plasma, related in part to inhibition of lipoprotein lipase [1,2]. Subsequent studies demonstrated that apo C-III may also interfere with apolipoprotein E-mediated clearance of triglyceride-rich lipoproteins from plasma. Apo C-III is primarily

synthesized by the liver, but a small amount is produced by enterocytes [3]. Apo C-III also contributes to hepatic very low-density lipoprotein (VLDL) synthesis and secretion.

In blood, apo C-III is primarily associated with the triglyceride-rich lipoproteins, chylomicrons and VLDL and their remnants, as well as high density lipoprotein (HDL) particles, but to a lesser extent with a subfraction of low-density lipoprotein (LDL) particles [4]. Apo C-III readily exchanges bidirectionally by diffusion between triglyceride-rich lipoproteins and HDL in relation to increasing and decreasing triglyceride levels related to fasting and feeding. During hydrolysis of triglycerides in triglyceride-rich lipoproteins, resulting in decreased size of the lipoprotein and clearance from plasma, apo C-III is transferred from VLDL and chylomicrons to HDL where it resides as a reservoir of apo C-III. During the postprandial state, in which triglyceride-rich chylomicrons are released into plasma via the thoracic duct, apo C-III is transferred from HDL back to triglyceride-rich lipoproteins. During lipolytic metabolism of VLDL particles, a proportion of VLDL-associated apo C-III is retained, resulting in formation of apo C-III containing LDL particles. In the context of normotriglyceridemia, most apo C-III in blood is carried by HDL particles [5,6].

2. Apo C-III and Atherosclerosis

Several lines of evidence have demonstrated that apo C-III containing lipoproteins have proinflammatory and proatherogenic properties that contribute to development of ASCVD [7]. It is well recognized that remnant lipoproteins have a causative role in development of ASCVD, which may be related in part to elevated levels of apo C-III [9]. The results of Mendelian randomization studies showed that loss of function pathogenic variants in apo C-III were associated with lower levels of triglycerides in blood and decreased risk of ASCVD, documenting the causative role of apo C-III in development of hypertriglyceridemia and ASCVD [10,11]. The apo C-III isoform varies among cohorts and may further modulate ASCVD risk [12]. These and other observations have stimulated interest in developing therapies to block apo C-III, but current development has focused on treatment of severe hypertriglyceridemia.

3. Familial Chylomicronemia Syndrome (FCS)

Familial chylomicronemia syndrome (FCS) is a rare genetically mediated condition that is caused by biallelic defects in the genes for either lipoprotein lipase (LPL) or the associated cofactors and regulatory proteins, apolipoprotein A-V (APOA5), apolipoprotein C-II (APOC2), lipase maturation factor-1 (LMF1), and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein-1 (GPIHBP1) [13].

Patients with FCS typically have severe hypertriglyceridemia with triglycerides > 1000 mg/dL, recurrent episodes of pancreatitis, and limited responsiveness to standard treatments for hypertriglyceridemia. The most severely affected individuals may have several episodes of pancreatitis annually, typically beginning in childhood. Among individuals with triglycerides persistently > 1000 mg/dL, less than 1–2% have FCS, with the remainder having multifactorial hypertriglyceridemia, but patients with the latter condition may also have increased risk for recurrent pancreatitis. In light of the refractory severe hypertriglyceridemia and high risk of potentially life-threatening recurrent pancreatitis, there has been an ongoing search for effective triglyceride-lowering treatments for patients affected by FCS.

4. Treatment for FCS

The core intervention for treatment of patients with FCS is marked restriction of dietary fat intake to < 10-15% of total energy intake and avoidance of alcohol intake. Traditional triglyceride-lowering therapies, such as fibrates, niacin, and fish oil products providing n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, are generally ineffective for triglyceride lowering in patients with FCS. Despite these interventions, many patients with FCS continue to experience recurrent pancreatitis and other troublesome symptoms of FCS, highlighting the great need for effective treatments for FCS.

Gene therapy was previously developed with the goal of restoring LPL activity in patients with FCS caused by pathogenic variants in the LPL gene. This led to the approval of alipogene tiparvovec, an adeno-associated virus type 1 (AAV1) vector, in 2012 by the European Medicines Agency (EMA). The drug was very expensive and required numerous intramuscular transfection injections. As a consequence of minimal clinical use due to the rarity of FCS and high cost of treatment, the drug was withdrawn from the market in 2017.

Evinacumab is a monoclonal antibody that binds angiopoietin-like 3 (ANGPTL3) in plasma and lowers the concentration of triglycerides and LDL-C. ANGPTL3 is an inhibitor of LPL and endothelial lipase, thereby interfering with lipolytic clearance of triglycerides from triglyceride-rich lipoproteins. Although evinacumab effectively lowers triglyceride levels in individuals who do not have FCS, it is ineffective for triglyceride lowering

in individuals with FCS, despite lowering the apo C-III concentration by >50% [14]. Other drugs that inhibit or block production of ANGPTL3 are in development for treatment of other conditions, but appear to be unlikely to be efficacious for treatment of patients with FCS. Evinacumab is currently Food and Drug Administration (FDA)-approved only for treatment to lower LDL-C in patients with homozygous familial hypercholesterolemia and is associated with an outstanding mean 49% decrease in LDL-C in this patient population with refractory severe hypercholesterolemia.

5. Drug Therapy Targeting Apo C-III

Aside from gene therapy, volanesorsen is the first drug that was developed and approved for treatment of patients with FCS. It is a second-generation antisense oligonucleotide (ASO) that blocks translation of apo C-III messenger ribonucleic acid (mRNA) and targets the mRNA for degradation by ribonuclease H1 (RNase H1). It lowers the plasma concentration of apo C-III by 70–80% in association with 65–75% reductions in triglyceride levels in patients with FCS [15]. Volanesorsen was approved in 2019 by the EMA for treatment of FCS, but there were concerns about the risk of thrombocytopenia that prevented approval by the FDA in the US. Subsequent efforts were devoted to modifying volanesorsen to improve potency and decrease side effects.

Olezarsen is an ASO derivative of volanesorsen that has an identical nucleic acid sequence, but is conjugated to N-acetylgalactosamine (GalNAc). The GalNAc modification increases hepatic targeting and drug potency, thereby facilitating decreased drug doses and reduced side effects. Key data from a pivotal study showed that monthly subcutaneous injections of olezarsen 80 mg in patients with FCS reduced apo C-III levels by 73.7% (95% confidence interval [CI] 52.8% to 94.6%) in association with triglyceride lowering by 43.5% (95% CI 17.9% to 69.1%, $p < 0.001$) from a baseline triglyceride concentration of 2630 ± 1315 mg/dL [16]. The incidence of pancreatitis was reduced by 88% with olezarsen compared to placebo (rate ratio [pooled olezarsen groups vs. placebo], 0.12; 95% CI, 0.02 to 0.66). Adverse event rates were similar for placebo and olezarsen [16]. Olezarsen was FDA-approved in December 2024 for treatment of adults with FCS and is a major breakthrough in pharmacotherapy for this patient population.

Plozasiran, also known as ARO-APOC3, is another apo C-III lowering drug that is still in phase 3 clinical development, but might receive FDA-approval in late 2025. In contrast to the ASO structure of olezarsen, it is an antisense small interfering RNA molecule that binds to apo C-III mRNA, thereby blocking translation of the mRNA and targeting the mRNA for degradation by the RNA-induced silencing complex (RISC). Seminal data from a phase 3 trial were published in January 2025. In this placebo-controlled trial, subcutaneous injections of plozasiran 25 and 50 mg administered every 3-months lowered the apo C-III concentration by ~90% and reduced median triglyceride levels by ~80% from a baseline concentration of 2044 mg/dL. The incidence of acute pancreatitis was reduced 83% (odds ratio, 0.17; 95% CI, 0.03 to 0.94; $p = 0.03$) in the pooled plozasiran groups compared to placebo [17]. The incidence of adverse events was similar with plozasiran and placebo. Other apo C-III blocking drugs that are in development in clinical trials include STT-5058, a humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to apo C-III in plasma, and other agents [3]. These data support the possibility that another potent triglyceride lowering agent that prevents pancreatitis may become available this year that will improve our capacity to treat patients with FCS and refractory severe hypertriglyceridemia.

6. Impact of Apo C-III Inhibition on Apo-B Containing Atherogenic Lipoproteins

Although patients with FCS tend to have low levels of apo B-containing atherogenic lipoproteins in plasma and correspondingly low risk of ASCVD, it is recognized that apo C-III may augment the atherogenicity of apo B-containing lipoproteins. Among patients with FCS, treatment with olezarsen was associated with a dose-dependent increase in LDL-C and non-significant change in apo B, but LDL-C levels remained low [16]. Similarly, treatment of patients with severe hypercholesterolemia with plozasiran in the SHASTA-2 trial was associated with a dose-dependent mean 60% increase in LDL-C, but apo B levels were unchanged and levels of non-HDL-C decreased [18]. In additional analyses of data from the SHASTA-2 trial and data from patients with combined hyperlipidemia in the MUIR trial, the LDL particle number (LDL-P) was unchanged by treatment with plozasiran, but large LDL-P increased by 53% and 88% in the two trials, respectively [19]. Small LDL-P trended down 13% and significantly decreased 38% in the two trials, respectively. Moreover, the triglyceride-rich particle number decreased 46% and 28% in the two studies, respectively, with decreases noted in all triglyceride-rich lipoprotein subclasses [19]. Similar changes in triglyceride-rich lipoprotein particle numbers, LDL-P and large LDL-P were observed in patients with ASCVD or increased risk of ASCVD and fasting triglycerides 200 to 499 mg/dL who were treated with olezarsen [20]. These findings suggested that inhibition of of Apo C-III in response to treatment

with olezarsen and plozasiran was associated with positive changes in triglyceride rich lipoproteins that may be associated with reduced risk of ASCVD, but further studies are needed to document whether these drugs may reduce ASCVD risk.

7. Conclusion

In conclusion, apo C-III is a key apolipoprotein that interferes with triglyceride metabolism and contributes to increased risk of ASCVD. Although apo C-III was identified more than 55 years ago, development of drugs targeting apo C-III has mostly been limited to the last two decades. The primary focus of current drug development has been on the rare disease indication for treatment of patients with FCS, but existing data demonstrate that the currently FDA-approved agent, olezarsen, and still experimental agent, plozasiran, that may be FDA-approved in November 2025, both are efficacious for triglyceride-lowering in other cohorts of patients with severe hypertriglyceridemia. The role of these agents for lowering levels of remnant lipoproteins and reducing risk of ASCVD remains to be determined, but it is anticipated that the indications for these drugs are likely to expand as additional clinical trial data are generated. In the meantime, it is an excellent clinical advance to now have available for clinical use a highly potent agent, olezarsen, for triglyceride lowering and prevention of pancreatitis in patients with FCS, with a second agent, plozasiran, potentially becoming available at the end of 2025. Although clinicians who treat patients with FCS are very grateful to have access to olezarsen for clinical use, the patients affected by FCS are particularly grateful that a long-awaited efficacious treatment is finally accessible that may reduce their suffering and improve their quality of life.

Funding

This research received no external funding.

Data Availability Statement

Not applicable.

Conflicts of Interest

Consultant and/or institutional grant funding from Ionis, Mirum/Travere, New Amsterdam, Novo Nordisk, Regeneron.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. Brown, W.V.; Levy, R.I.; Fredrickson, D.S. Studies of the proteins in human plasma very low-density lipoproteins. *J. Biol. Chem.* **1969**, *244*, 5687–5694.
2. Brown, W.V.; Baginsky, M.L. Inhibition of lipoprotein lipase by an apoprotein of human very low-density lipoprotein. *Biochem. Biophys. Res. Commun.* **1972**, *46*, 375–382.
3. Packard, C.J.; Pirillo, A.; Tsimikas, S.; et al. Exploring apolipoprotein C-III: Pathophysiological and pharmacological relevance. *Cardiovasc. Res.* **2024**, *119*, 2843–2857.
4. Taskinen, M.R.; Borén, J. Why is apolipoprotein C-III emerging as a novel therapeutic target to reduce the burden of cardiovascular disease? *Curr. Atheroscler. Rep.* **2016**, *18*, 59.
5. Fredenrich, A.; Giroux, L.M.; Tremblay, M.; et al. Plasma lipoprotein distribution of apo C-III in normolipidemic and hypertriglyceridemic subjects: Comparison of the apo C-III to apo E ratio in different lipoprotein fractions. *J. Lipid Res.* **1997**, *38*, 1421–1432.
6. Yamazaki, A.; Ohkawa, R.; Yamagata, Y.; et al. Apolipoprotein C-II and C-III preferably transfer to both high-density lipoprotein (HDL)2 and the larger HDL3 from very low-density lipoprotein (VLDL). *Biol. Chem.* **2021**, *402*, 439–449.
7. Ginsberg, H.N.; Packard, C.J.; Chapman, M.J.; et al. Triglyceride-rich lipoproteins and their remnants: Metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. *Eur. Heart J.* **2021**, *42*, 4791–4806.
8. Do, R.; Willer, C.J.; Schmidt, E.M.; et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat. Genet.* **2013**, *45*, 1345–1352.
9. Nordestgaard, B.G. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: New insights from epidemiology, genetics, and biology. *Circ. Res.* **2016**, *118*, 547–563.

10. Jorgensen, A.B.; Frikke-Schmidt, R.; Nordestgaard, B.G.; et al. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N. Engl. J. Med.* **2014**, *371*, 32–41.
11. The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N. Engl. J. Med.* **2014**, *371*, 22–31.
12. Sinari, S.; Koska, J.; Hu, Y.; et al. Apo CIII Proteoforms, Plasma Lipids, and Cardiovascular Risk in MESA. *Arterioscler. Thromb. Vasc. Biol.* **2023**, *43*, 1560–1571.
13. Baass, A.; Paquette, M.; Bernard, S.; et al. Familial chylomicronemia syndrome: An under-recognized cause of severe hypertriglyceridaemia. *J. Intern. Med.* **2020**, *287*, 340–348.
14. Rosenson, R.S.; Gaudet, D.; Ballantyne, C.M.; et al. Evinacumab in severe hypertriglyceridemia with or without lipoprotein lipase pathway mutations: A phase 2 randomized trial. *Nat. Med.* **2023**, *29*, 729–737.
15. Witztum, J.L.; Gaudet, D.; Freedman, S.D.; et al. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. *N. Engl. J. Med.* **2019**, *381*, 531–542.
16. Stroes, E.S.G.; Alexander, V.J.; Karwatowska-Prokoczuk, E.; et al. Olezarsen, acute pancreatitis, and familial chylomicronemia syndrome. *N. Engl. J. Med.* **2024**, *390*, 1781–1792.
17. Watts, G.F.; Rosenson, R.S.; Hegele, R.A.; et al. Plozasiran for managing persistent chylomicronemia and pancreatitis risk. *N. Engl. J. Med.* **2025**, *392*, 127–137.
18. Gaudet, D.; Pall, D.; Watts, G.F.; et al. Plozasiran (ARO-APOC3) for Severe Hypertriglyceridemia: The SHASTA-2 Randomized Clinical Trial. *JAMA Cardiol.* **2024**, *9*, 620–630.
19. Ballantyne, C.M.; Gaudet, D.; Rosenson, R.S.; et al. Effect of Targeting apoC-III with Plozasiran on Lipoprotein Particle Size and Number in Hypertriglyceridemia. *J. Am. Coll. Cardiol.* 2025, *in press*. https://doi.org/10.1016/j.jacc.2025.03.496.
20. Karwatowska-Prokopczuk, E.; Tardif, J.C.; Gaudet, D.; et al. Effect of olezarsen targeting APOC-III on lipoprotein size and particle number measured by NMR in patients with hypertriglyceridemia. *J. Clin. Lipidol.* **2022**, *16*, 617–625.