Silencing APOC3: A Novel Olezarsen Therapy in Familial Chylomycronemia Syndrome

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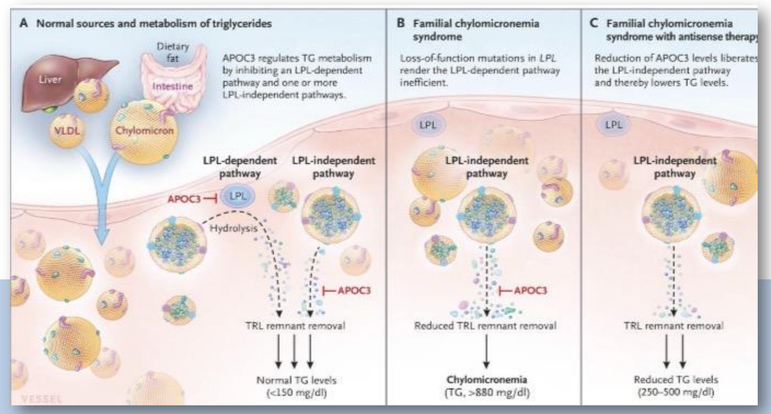
Introduction

Familial Chylomicronemia Syndrome (FCS) is a rare autosomal recessive disorder characterized by severe hypertriglyceridemia due to impaired clearance of chylomicrons. Most cases result from biallelic pathogenic variants in genes essential for lipolysis, most commonly LPL, but also APOC2, APOA5, GPIHBP1, or LMF1. APOA5 is thought to stabilize the LPL–lipoprotein complex, and rare mutations that abolish apoA-V function lead to classic FCS with severely impaired lipolysis. Patients present with fasting hypertriglyceridemia (>885 mg/dL), recurrent pancreatitis, eruptive xanthomas, and lipemia retinalis. Heterozygous carriers may exhibit variable phenotypes depending on environmental and genetic modifiers. The condition is frequently underrecognized due to diverse clinical presentations including xanthomas, hypercholesterolemia, thrombocytopenia, or hemolytic anemia, sometimes leading to misdiagnosis. Epidemiologic data show FCS remains exceedingly rare across populations, including Latinos, with prevalence estimates of <0.05% among those with triglycerides >880 mg/dL. Early recognition is critical since conventional lipid-lowering therapies such as fibrates often prove ineffective, given their reliance on upregulating functional LPL. Novel therapies such as antisense oligonucleotides and small interfering RNA targeting APOC3 offer promising new options by enhancing triglyceride clearance. Timely diagnosis and intervention are essential to prevent complications and improve quality of life.



Targeting APOC3 in the Familial Chylomicronemia Syndrome. Published December 4, 2014 N Engl J Med 2014;371:2200-2206. DOI: 10.1056/NEJMoa1400284

Case

This case report involves a 37-year-old Puerto Rican female referred to our endocrinology clinic by her cardiologist for evaluation of persistent hypertriglyceridemia since childhood. She was managed with fenofibrate 160 mg daily and omega-3 fatty acids 2 g daily. Family history was significant for hypertriglyceridemia and pancreatitis in her mother, without premature cardiovascular disease. Physical exam revealed no eruptive xanthomas or lipemia retinalis. Laboratory evaluation showed total cholesterol 283 mg/dL and triglycerides 1117 mg/dL, with normal liver function tests, hematology and platelets. ApoB levels were elevated at 114 mg/dL. A genetic panel identified a heterozygous mutation in APOA5 (c.56C>G, p.(Ser19Trp)), confirming the diagnosis of FCS. Nutritional counseling and a very low-fat diet (< 20 g/day) were initiated. Pharmacologic management included olezarsen 80 mg subcutaneous monthly. Olezarsen, exerts its effect by binding APOC3 mRNA, reducing APOC3 protein synthesis, thereby disinhibiting LPL and improving triglyceride clearance. Follow-up lipid panels were obtained at baseline and after therapy initiation. After one week of therapy, lipid profile demonstrated improvement with triglycerides reduced to 749 mg/dL, total cholesterol 319 mg/dL, and HDL-C 43 mg/dL. This represented approximately a 70% reduction in triglyceride levels within the first month, surpassing reductions reported in the BALANCE trial, where olezarsen demonstrated significant triglyceride lowering in patients with hypertriglyceridemia. This outcome underscores the therapeutic potential of targeting APOC3 in patients with genetically mediated chylomicronemia syndromes, even when heterozygous variants are involved. Conventional pharmacotherapies, such as fibrates, are largely ineffective in this population due to their reliance on functional LPL activity. Olezarsen, by directly downregulating APOC3, bypasses the genetic impairment and restores triglyceride metabolism, offering a targeted approach.

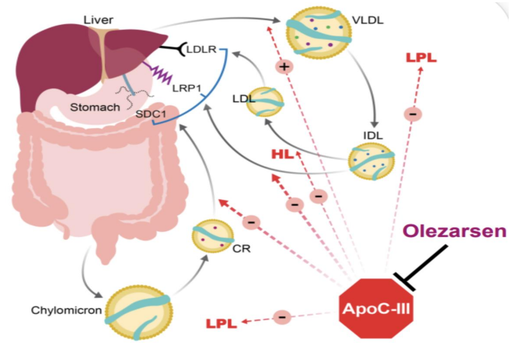


Image adapted from: Gordts PL, et al J Clin Invest. 2016;126:2855

Laboratories

137	102	12	91
4.7	25	0.68	

6.3	12.6	245	
	37.6%		

HA1C: 5.32%
ALT: 20 U/L
AST: 23 U/L
Lp(a): 76.9 mg/dL
NT-pro BNP: < 20 pg/mL
NAFCS: 45
Moulin European Score: 13

Lipid Profile:
Total Cholesterol: 283 mg/dL
Triglycerides: 1117 mg/dL
HDL-C: 42 mg/dL

ApoA-1: 153 mg/dL
(normal range: <= 116 mg/L)

ApoB: 114 mg/dL
(normal range: <= 90 mg/L)

Conclusion

For clinical practice, this case highlights the need for heightened awareness among clinicians to consider genetic dyslipidemias in young patients with severe, persistent hypertriglyceridemia. For future research, larger studies are warranted to evaluate olezarsen efficacy across diverse populations and genetic variants, including Hispanic cohorts, and to assess long-term cardiovascular outcomes. Expanding genetic screening and improving access to novel lipid-lowering therapies will be crucial to reducing morbidity and improving quality of life for patients with FCS worldwide.