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Research

New Therapeutic Approaches to Familial Chylomicronemia Syndrome (FCS)

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I. Introduction

Familial chylomicronemia syndrome (FCS) is a rare disorder caused by impaired lipoprotein lipase (LPL), an enzyme that normally cleaves triglycerides (TGs) in the plasma. As a result, FCS patients present with extremely elevated TGs, caused by a buildup of chylomicrons. Chylomicrons (CM) are TG-rich lipoproteins that transport exogenous or dietary lipids from the small intestines to rest of the body. In unaffected individuals, lipoprotein lipase breaks down chylomicron-TG; however, absent functional LPL, chylomicrons accumulate in the blood, causing elevated triglycerides. LPL also catabolizes VLDL-TG, another TG-rich lipoprotein. VLDL transports endogenous lipids from the liver to rest of the body. Together, VLDL and chylomicrons are referred to as TG-rich lipoproteins (TRLs).

The most common cause of FCS is a detrimental mutation in the LPL gene. The functionality and maturation of LPL depends on numerous co-factors and regulatory proteins. Secreted as a monomer, LPL pairs unite as an active dimer under the influence of lipase maturation factor-1 (LMF-1). Absent LMF-1, LPL fails to dimerize and is rapidly degraded[6]. Once the LPL dimer is prepared, it is transported to the luminal surface of the endothelium and is anchored to the surface by glycosylphosphatidylinositol, a high-density lipoprotein binding protein 1 (GPIHBPI-1)[7]. For the LPL dimer to fully interact with lipoproteins, activation also requires it to bind with the co-factor apolipoprotein C2 (apoC2). ApoA5 also plays a vital role to help hydrolyze triglycerides by enhancing LPL's activity[4].

Each of these co-factors and regulatory proteins are essential for LPL functioning. Disabling mutations in LMF-1, GPIHBP1-1, apoC2, and apoA5 will therefore impair LPL activity leading to FCS. High levels of CMs may manifest as eruptive xanthomas, hepatosplenomegaly and/or lipemia retinalis. However, the most serious clinical manifestation of FCS is acute pancreatitis. Recurrent acute pancreatitis is thought to occur in FCS patients due to

the accumulation of CMs in the pancreatic capillaries, which results from lipolysis by pancreatic lipase[4].

Since CM clearance is steadily impaired, TG levels will remain elevated despite fasting. FCS is usually suspected in patients with elevated TGs (>1000 mg/dL) in three consecutive fasting specimens. A ratio of total triglyceride to total cholesterol (TG/TC) is a hallmark of FCS. Specifically, a TG/TC ratio above 5 (mg/dL)/(mg/dL) or above 2.2 (mmol/L)/(mmol/L) indicates a high level of circulating CMs, suggesting a diagnosis of FCS. In addition, apoB is usually less than 75 mg/dL in FCS.

Currently, there is no effective medical treatment for FCS. Restriction of dietary fat content (20-25 g/day) is the mainstay management, but long-term compliance is difficult to maintain. Other TG-lowering agents such as fibrates and omega-3 fatty acids are often not very effective in treating FCS[4]. Currently, there are many new therapeutic approaches in development for the treatment of FCS. To simplify and organize these new therapeutic agents, we categorized them according to their major mechanism: retarding TG or TRL synthesis or hastening TG or TRL catabolism (Fig 1).

II. Causes of FCS

Chylomicronemia is defined by the persistent presence of chylomicrons in plasma after a fasting period of 12-14 hours. Normally, chylomicrons are cleared from plasma within 3-4 hours. Presence of chylomicronemia is associated with triglyceride levels of >180 mg/dL.
FCS is usually caused by a disabling mutation of one or more genes associated with the clearance and lipolysis of chylomicrons. It often presents in infancy or childhood, but some forms present by adolescence, and others later in life. LPL is the most common gene causing FCS[4]. There are many types of LPL mutations including frame shift, missense, and nonsense mutations; however, no single mutation predominates. As a result of a mutation in LPL, chylomicrons accumulate, driving clinical features. Although LPL mutations are the most prevalent cause, mutations in apoC2, apoA5, LMF-1, and GPI-HBP1 can also cause FCS[5].

ApoC2 is an important co-factor for LPL and is a necessary component of the enzyme's activity. Consequently, LPL function is inhibited when functional apoC2 is lacking. A defect in apoA5 will also inhibit LPL activity, as apoA5 enhances LPL function. LMF-1 is lipase maturation factor-1 that makes inactive LPL monomers into active dimers. A defect in LMF-1 will impair dimerization, prompting rapid degradation of LPL monomers[6]. Finally, GPIHBP1 transports and anchors LPL onto endothelial luminal surface[7]. Loss of function in GPIHBP1 will thereby hinder LPL activity, causing FCS.

III. Diagnosis

Currently, there are several diagnostic algorithms proposed to distinguish FCS from more common causes of chylomicronemia. The Fredrickson classification of lipid disorders describes the criteria for the diagnosis and determination of hyperlipidemias. Since FCS mainly affects the metabolism CMs, it is classified as Frederickson hyperlipidemia Type I, or Pure

Chylomicronemia. Type V or Mixed Chylomicronemia is a disorder that affect both CMs and VLDL.

Phenotype	**Elevated lipoprotein**	**Elevated lipid**
I	CM	TG and TC
V	CM and VLDL	TG and TC
IV	VLDL	TG and normal-moderate increases in TC
III	Floating β-lipoproteins	TG and TC
IIb	LDL and VLDL	TG and TC
IIa	LDL	TC

Table 1. Frederickson phenotype classification[27]
CM (chylomicrons); *LDL* (low density lipoprotein); *TC* (total cholesterol); *TG* (triglyceride); *VLDL* (very low-density lipoprotein)
TG > 880 mg/dL or > 10 mmol/L on three separate tests and/or TG/Cholesterol ratio > 5 (mg/dL)/(mg/dL) or > 2.2 (mmol/L)/(mmol/L) will indicate FCS.

Site of Ectopic TG Deposition	**Symptoms**
Pancreatic Capillaries	Pancreatitis
Skin	Xanthomas
GI Macrophages	Hepatosplenomegaly
Retinal Vessels	Lipemia Retinalis

Table 2. Clinical Presentation of Extreme Triglyceridemia involving Chlyomicronemia (All, Some or None)

A blood sample from an FCS patient often has a latescent or "milky" appearance due to the excess chylomicrons present in their blood. To check for CM concentration, a "refrigerator test" is performed. After chilling a blood sample overnight, CMs will appear as a creamy supernatant[4]. The best way to differentiate between a Type I (Pure Chylomicronemia) and Type V diagnosis is by measuring apoB levels, or by measuring the patients TG/apoB ratio. A Type V (Mixed Chylomicronemia) patient will present with an apoB level above 120 mg/dL. Additionally, a Type I patient will present with a low to normal level of apoB (<100 mg /dL). Additionally, Type I patients will have a TG/apoB ≥8.8 (mg/dL)/(mg/dL) or ≥10 (mmol/L)/(g/L) [28]. Therefore, apoB serves as a biochemical parameter to differentiate between the two metabolic disorders.

In addition, the ApoB app, currently available for free on Google Play and the Apple Store, allows physicians to easily identify which particles are elevated by inputting the total cholesterol, TG, and apoB levels. This app allows the physician to differentiate between hyperlipidemia classes from elevated VLDL particles, remnant particles, and CMs[4]. Alternative methods of differential diagnosis include traditional lipid electrophoresis or ultracentrifugation to assess the Frederickson class.

A genetic disorder must be confirmed by gene sequencing of apoE, LPL, apoC2, apoA5, LMF-1, and GPIHBP-1. If a mutation is found, then a diagnosis of FCS is confirmed. If, however, no mutation is found then additional analysis must be done in order to rule FCS in or out. Post-heparin should reveal severely diminished LPL activity.

IV. Current therapy

Restriction of dietary fat intake (20-25 g/day) is the only reliable treatment of FCS at this point. Successful fat restriction usually improves xanthomas and hepatosplenomegaly, and reduces the risk of acute pancreatitis[5]. However, this dietary regimen is difficult to maintain and long-term compliance is poor in many patients. In addition, traditional TG-lowering agents such as fibrates and fish oil have a limited impact on patients with FCS as previously mentioned. Apart from FCS, fibrates inhibit apolipoprotein (apoC3) which reduces the formation of VLDL but not CMs. ApoC3 counterbalances the stimulatory effect of apoC2, and thus inhibits LPL. Fibrates inhibit apoC3, thus disinhibiting LPL-meditated lipolysis and reducing total triglyceride levels up to 50%[5]. However, since LPL function is compromised in patients with FCS, the fibrates underperform.

Niacin was demonstrated to lower cholesterol and TG and raise HDL. It became common practice to treat hypercholesterolemia to prevent MI by administering immediate-release niacin at a maximum dose of 2g/day or the longer-releasing niacin pro-drug, pentaerythirtyl tetranicotinate[29]. Niacin also inhibits the function of diacylglycerol-O-acyltransferase 2 (DGAT2), which decreases the formation of hepatic VLDL[10, 11]. Unfortunately, niacin often causes unpleasant side effects such as flushing, light-headedness and pruritus. On average, the TG lowering impact of niacin is about 5% to 35%. However, its efficacy in FCS patients is still unknown[4].

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitors that do not have much of a TG lowering effect on FCS patients. However, statins do increase the catabolism of CM remnants. They are often used concurrently with ezetimibe, a drug that lowers plasma cholesterol levels. Together, statins and ezetimibe can be used to reduce TG-rich lipoproteins[12].

High doses of omega-3 fatty acids (4-6g) inhibit hepatic VLDL production, increase lipolysis, and increase chylomicron clearance. They may operate by inhibiting apoC3. The potential effectiveness of omega-3 fatty acids in FCS has not been vigorously tested; therefore their efficacy is unpredictable in FCS.

Another therapy involves directly removing VLDL and chylomicrons by plasmapheresis or plasma exchange. However, plasmapheresis is costly, requires specialized staff and exposure to blood products, and only temporarily improves TG levels. It is typically used in the setting of an admission for acute pancreatitis to rapidly lower TGs. It is especially helpful to exchange with donor plasma when the patient has FCS from apo-C2 deficiency because there is enough apo-c2 protein from the donor to temporarily reverse apo-C2 deficiency.

V. Emerging Therapy

We organized novel therapies by whether they primarily alter synthesis vs. catabolism of TG and TG-rich lipoproteins. The figure that we developed portrays the different therapies into four quadrants:

1) Retarding TG-synthesis
2) Retarding TRL-synthesis
3) Hastening TG-catabolism
4) Hastening TRL-catabolism

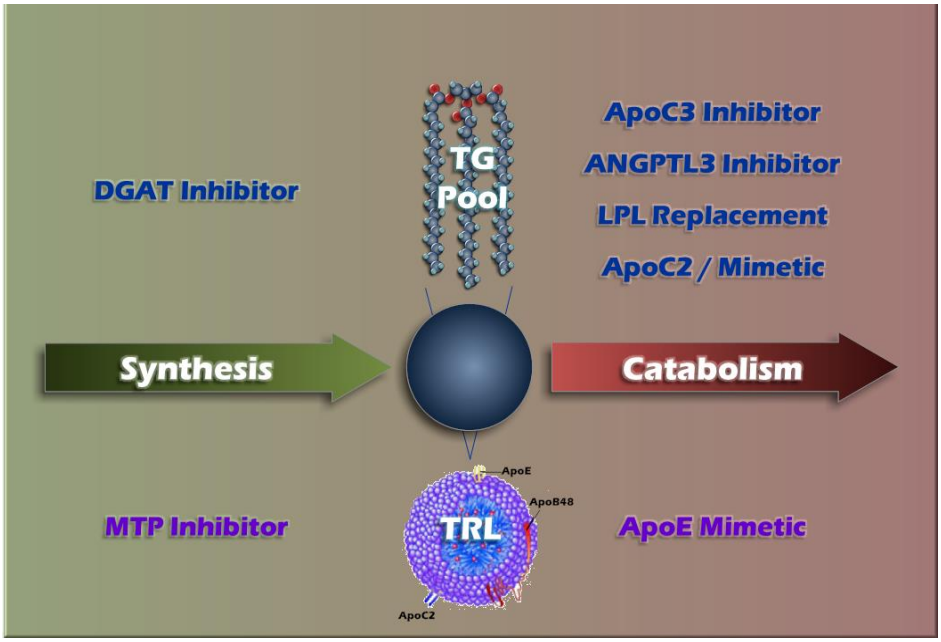

Figure 1. Potential therapies for FCS

a. Retarding Triglyceride Synthesis

Diacylglycerol O-acyltransferases (DGATs) meditate TG synthesis and re-synthesis after dietary absorption. They are mainly expressed in gut, liver, and adipose tissues. Therefore, DGAT inhibitors should lower the synthesis of TG. In recent studies of an experimental DGAT inhibitor (AZD7687), subjects experienced severe side-effects such as nausea, vomiting and diarrhea[14]. In subsequent studies, the dose was reduced to avoid gastrointestinal side effects, but this ultimately undermined the efficacy of the drug. Another oral DGAT1 inhibitor, Pradigastat, showed promising results: TGs reduction of 70-80% with no obvious adverse effects in three individuals with FCS[15].

b. Retarding Triglyceride Rich Lipoprotein Synthesis

Microsomal triglyceride transfer protein (MTP) assembles CMs and VLDL. Lomitapide inhibits MTP and is currently approved in North America and Europe to treat homozygous familial hypercholesterolemia. Fortuitously, it lowers TG by 30-40%[16-19]. Lomitapide targets MTP in the liver and intestine to prevent the transfer of TGs and other lipids to apoB-containing lipoproteins, including CMs. However, this drug has adverse GI effects: notably nausea, vomiting and diarrhea[17]. Furthermore, Lomitapide causes a transient increase in liver enzymes and an increase in hepatic fat content, which increases risk for steatohepatitis.

Lipoprotein lipase is the main digestive enzyme that degrades TGs into fatty acids and glycerol. Therefore, we expect that disinhibiting any LPL inhibitors will increase TG degradation and ultimately decrease TGs.

ApoC3 is a major component of triglyceride-rich lipoproteins (TRLs) and counteracts the stimulatory effect of apoC2 on LPL, thus inhibiting LPL indirectly. Conversely, disrupting apoC3 increases LPL activity in turn lowering TGs. An antisense oligonucleotide targeting apoC3 mRNA is currently in development to treat FCS. A phase I clinical trial in healthy human subjects showed that the antisense oligonucleotide targeting apoC3 mRNA reduced plasma apoC3 77% and TGs 43% with no major adverse effects[20]. Finally, apoC3 inhibition also improved insulin sensitivity. Among diabetics with high TGs, improvement of insulin sensitivity was strongly correlated to the drop in TGs ($r= -0.68$, $P=0.01$)[30]. This raises the hope that novel therapies that profoundly lower TGs may thereby improve carbohydrate metabolism. Angiopoietin-like protein 3 (ANGPTL3) is mainly expressed in liver and acts to reversibly inhibit LPL and endothelial lipase (EL). LPL inhibition raises TGs, and EL inhibition raises high-density lipoprotein (HDL). ALN-ANG, an antisense oligonucleotide that inhibits translation of ANGPTL3 mRNA, lowered cholesterol and triglycerides in preclinical trials[21]. Therefore, the ANGPTL3 inhibitor disinhibits LPL to increase TG catabolism. Further development of this agent is still in process.

If a patient presents with a genetic defect in LPL itself, then introducing a functional LPL gene could relieve FCS symptoms. Currently, there is only one gene therapy treatment approved for the treatment of FCS. Alipogene tiparvovec (Glybera) is an LPL replacement therapy utilizing the adeno-associated viral vector 1 (AAV1) combined with gain-of-function LPL to deliver a functional copy of LPL to LPL deficient patients[22-25]. This is currently approved in Europe but not in North America. Alipogene tiparvovec is administered as series of intramuscular injections under spinal anesthesia. After 12 weeks, the therapy significantly reduces fasting TGs with no major adverse events. However, fasting TGs transiently decrease after treatment and return to baseline about 5 months post initial injection[22, 23]. More importantly, there were durable improvements in chylomicron kinetics, a reduced incidence of pancreatitis and clinical benefits of improved energy levels. However, *LPL* gene therapy is only appropriate for patients with a *LPL* gene mutation and it is not beneficial in patients with functional LPL. Despite promising proof-in-concept, the drug was withdrawn from the market due its high cost, abandoning the therapy and FCS patients along with it.

Another agent that may help increase the activity of LPL is an apoC2 mimetic. ApoC2 is a critical co-factor for LPL and essential to the proper function of LPL. Since one of the more

common causes of FCS is apoC2 deficiency, infusing apoC2 potentiates LPL, thereby lowering TGs. This is easily done by giving fresh frozen plasma (FFP) and it can be given outright or as therapeutic plasma exchange (TPE) with FFP during a pancreatitis admission. This can also be used in the ambulatory setting to prevent recurrent pancreatitis. Currently, an apoC2 mimetic peptide is in pre-clinical development[31].

c. Hastening Triglyceride Rich Lipoprotein Catabolism

Apolipoprotein E (apoE) is a ligand for hepatic receptors to clear apoB lipoprotein remnants (i.e., CM and VLDL remnant). As a result, apoE hastens TRL catabolism. ApoE has two distinct functional domains: the highly reactive heparin-binding domain at both N- and C-terminals. The N-terminal is the receptor-binding domain, and C-terminal contains a highly hydrophobic domain that inserts onto the surface of lipoproteins[2].

d. Summary

Familial chylomicronemia syndrome (FCS) results from impaired LPL activity due to mutations in LMF-1, GPIHBP1, apoC2, and apoA5. LMF-1 promotes LPL dimerization, GPIHBP1 transports and anchors active LPL onto endothelial luminal surface, apoC2 is a critical co-factor for LPL function, and apoA5 further enhances the activity of LPL.
At present, the only reliable treatment for FCS is dietary fat restriction. However, long term compliance of dietary restrictions is hard to maintain, and thus leaves much to be desired. Moreover, traditional lipid lowering drugs, such as fibrates, niacin, omega-3 fatty acids, and statins, have unpredictable efficacy in FCS patients.

VI. Future Studies

Considerations for other therapeutic approaches to FCS involve inhibiting apoB, as well as other agents that inhibit sterol regulatory element-binding protein (SREB). Inhibition of apoB will lower TRL (CM & VLDL) synthesis and inhibition of SREB will hasten LPL activity. Mipomersen is an antisense oligonucleotide inhibitor of apoB (including apoB-48) indicated to treat homozygous familial hypercholesterolemia[3]. The antisense oligonucleotide therapy acts to inhibit the gene expression by binding to the native complimentary mRNAs and as a result, it prevents translation of native gene products[27]. In addition to its role in reducing the synthesis and secretion of apoB-containing lipoproteins, Mipomersen decreases the synthesis and secretion of apoC3 and apoC3-containing lipoproteins, which may have added benefits for FCS patients[3]. Common adverse effects include injection site reaction and flu-like symptoms[3]. However, similarly to Lomitapide, the drug can increase liver transaminases has a black box label warning for serious risk of liver damage and a risk management plan is necessary[32]. This presents a significant barrier for use as a treatment method for FCS.

CAT-2003 is a niacin and eicosapentaenoic acid (EPA) conjugate that inhibits the maturation of sterol regulatory element-binding protein (SREB) and as a result, increases LPL activity and TG clearance. Niacin and EPA are linked in a way that bypasses GPR-109A receptor, thus averting niacin-associated skin toxicity. It works by decreasing the cAMP production on a molecular level to achieve this. The GPR-109A receptor has a high affinity for niacin, and once bound and activated, inhibits lipolytic and atherogenic activity, normalizing lipoprotein profiles[33]. Sterol regulatory element-binding protein transcribes many inhibiting

factors of LPL including apoC3, ANGPTL3, ANGPTL4, and PCSK9. CAT-2003 inhibits the production of these factors which increases LPL activity. Clinical trials of this compound have demonstrated its safety and tolerance. There is also evidence that CAT-2003 reduces apoB-containing lipoproteins and PCSK9, which results in a reduction of postprandial and fasting trigylcerides[1]. It is currently in phase II as a potential new agent for managing chylomicronemia[1].

VII. Conclusion

The understanding of FCS has advanced tremendously over the years, enabling us to find better alternatives in an otherwise undertreated population. The treatment revolves around an extremely low-fat diet, although patients find this difficult to maintain. There are many promising emerging approaches to FCS such as apoC3 inhibitors, ANGPTL3 inhibitors, LPL gene therapy, MTP inhibitors, DGAT inhibitors, apoC2 mimetics, and apoE mimetics. Several agents remain in development and may never prove useful for FCS, and despite several setbacks we remain hopeful that significant relief is on the way for our FCS patients.

VIII. References

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