Familial chylomicronemia syndrome: A comprehensive clinical and genetic approach

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Abstract

The familial chylomicronemia syndrome (FCS) is characterized by very high levels of circulating triglycerides. FCS is caused by lipoprotein lipase (LPL) deficiency resulting from homozygous or biallelic loss-of-function variants in the *LPL* or other related genes. Here, we report a case of severe hypertriglyceridemia refractory to conventional therapy in a male patient diagnosed at 33 years of age. LPL activity was below 20%. During the clinical course, the patient developed severe acute pancreatitis in addition to other complications. Two heterozygous variants (c.984G>A and c.1139+6T>C) which had not been previously reported in the major databases were identified in the *LPL* gene. Treatment with volanesorsen was proposed based on its approved indication as an adjunct to diet in adult patients with confirmed FCS and at high risk for pancreatitis. Volanesorsen was effective and well-tolerated, and the patient did not experience abdominal pain or any other manifestations. The assessment of genetic characterization is essential to guide treatment decisions during follow-up, in addition to the patient's history, their comorbidities and clinical stigmas.

Keywords

Familial chylomicronemia syndrome, hypertriglyceridemia, volanesorsen

Introduction

The familial chylomicronemia syndrome (FCS), also known as lipoprotein lipase deficiency or Fredrickson type I hyperlipidemia due to the characteristic pattern of chylomicron accumulation observed on agarose gel, is a rare genetic lipid disorder characterized by very high levels of circulating triglycerides (TG) [1].

FCS is associated with a markedly impaired lipoprotein lipase (LPL) function due to homozygous or biallelic loss-of-function variants of the *LPL* [2] or other genes implicated in the LPL function, including *APOC2, APOA5, GPIHBP1* and *LMF1* [3,4]. Most patients with severely deficient LPL are diagnosed in early childhood or young adulthood, although phenotypic features can be present in affected individuals at any age [3]. The deficiency or absence of LPL activity leads to the buildup of chylomicrons in plasma and severe hypertriglyceridemia; fasting TG levels can be 10- to 100-fold higher among patients with FCS compared to healthy subjects [1]. These patients can develop a range of signs and symptoms, including eruptive xanthomata, *lipemia retinalis*, hepatosplenomegaly and abdominal pain. The most serious complication is acute pancreatitis, which is often recurrent and related to severe hypertriglyceridemia. Of note, elevated TG levels are correlated with a poor prognosis in patients with pancreatitis [5].

FCS affects 1 in every 100,000 to 1,000,000 individuals worldwide, although the estimation of its actual prevalence remains a challenge as in every rare condition [4].

Clinical Case

We present a male patient who had been diagnosed with hypertriglyceridemia at 33 years of age (TG: 2000 mg/dL [upper limit of normal: 150 mg/dL]). His remarkable medical history included recurrent episodes of abdominal pain since early childhood. In 2002, the patient was tested in the Lipids and Lipoproteins Lab of the University of Buenos Aires and LPL activity was found to be below 20% (modified Nilsson-Ehle

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method in a post-heparin sample with a radioactive substrate). In addition to lifestyle changes (weight control, reduced intake of saturated and unsaturated fats [less than 10% of total daily energy] and physical exercise plan), the patient received several combinations and doses of gemfibrozil, ciprofibrate, statins, ezetimibe and omega-3 fatty acids, but TG levels remained persistently high.

On subsequent visits, the patient was also diagnosed with elevated fasting blood glucose levels, with a rapid progression to type 2 diabetes mellitus, and started treatment with metformin and, eventually, insulin glargine.

During the clinical course, the patient reported repeated episodes of abdominal pain and was inconsistently followed, until at 45 years of age he presented to the emergency department complaining of acute and unbearable abdominal pain. He was diagnosed with acute pancreatitis (APACHE score 2), with a TG level of 1281 mg/dL at admission. An initial CT scan revealed rounded hypodense lesions in the body and tail of the pancreas, probably consistent with cysts, without peripancreatic collections. Splenomegaly was also documented (168 mm). An ultrasound exam showed dilation of the common bile duct (118 mm). A magnetic resonance cholangiography confirmed the presence of residual choledocholithiasis and an endoscopic retrograde cholangiopancreatography (ERCP) was required. Hemoglobin and hematocrit levels at discharge were 13 g/dL and 37.5%, respectively.

Six months later, the patient was admitted to hospital due to biliary obstruction. He was diagnosed with common bile duct stenosis and a biliary stent was placed.

During follow-up, hypertriglyceridemia (TG: 2800 mg/dL) and diabetes mellitus (fasting blood glucose: 260 mg/dL; glycosylated hemoglobin: 8.7%) were poorly controlled despite treatment with fenofibrate (200 mg/day), insulin glargine (basal 10 U/day), metformin (875 mg bid) and omega-3 fatty acids (8 g/day).

The patient reported no abdominal manifestations for a long period of time and no new follow-up visits were recorded. He returned to a visit with his sister, who also had a history of hypertriglyceridemia, and was then referred to our unit. Following a clinical and laboratory reassessment, next-generation sequencing (NGS) was performed for genes associated with FCS (*LPL, APOC2, APOA5, GPIHBP* and *LMF1.2*). Both heterozygous variants c.984G>A and c.1139+6T>C were detected in the *LPL* gene.

The clinical significance of mutations in the *LPL* gene was reported to be uncertain; however, based on the patient's medical records, the severity of the episodes of pancreatitis, treatment resistance and the history of LPL levels below 20%, these mutations were considered to be significant in this context given the clinical behavior of the disease.

The patient was started on weekly subcutaneous administration of volanesorsen 285 mg. Telephone follow-up calls were made to monitor outpatient treatment administration at home. A rapid reduction of 62% was observed in plasma TG levels (Figure 1). Platelet counts were monitored during follow-up; despite TG levels were initially reduced, especially during the first six months of treatment, a plateau was subsequently reached. The patient received a single short cycle of corticosteroids when thrombocytopenia was confirmed (platelet count <50x10^9/µL) and achieved a rapid response (Figure 2).

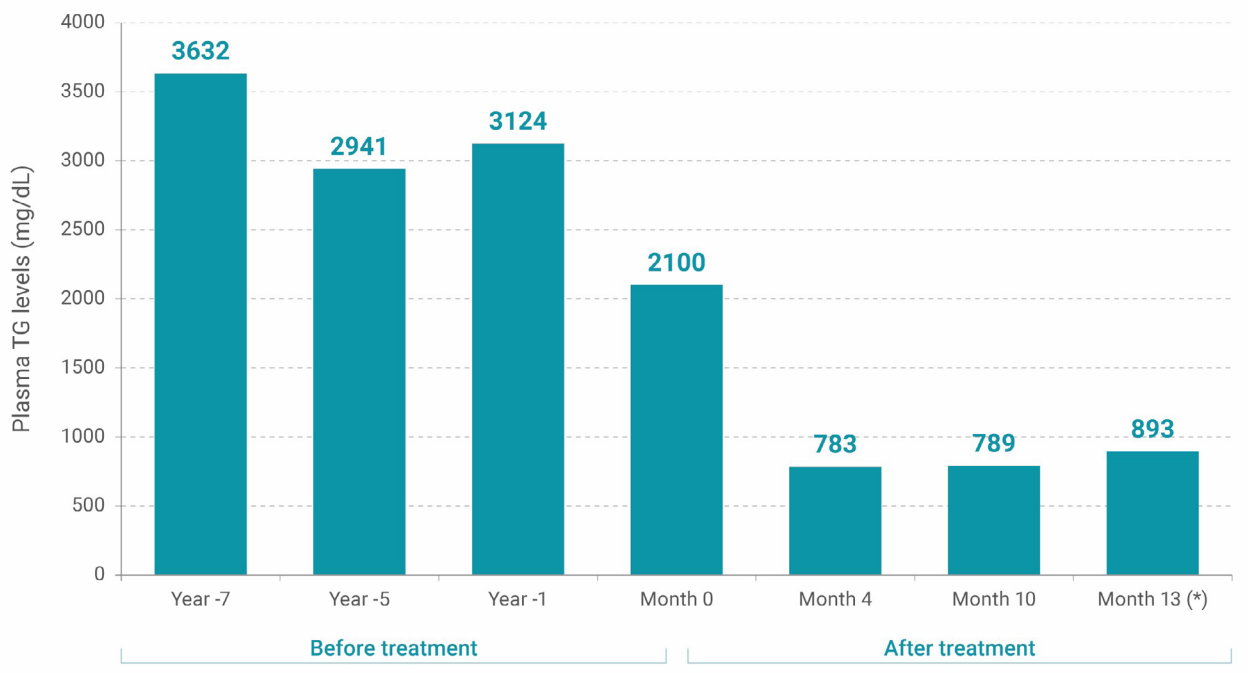

Figure 1. Fasting plasma TG levels before and after treatment with volanesorsen.
(*) The transient increase was associated with the brief discontinuation of treatment due to elevated transaminases

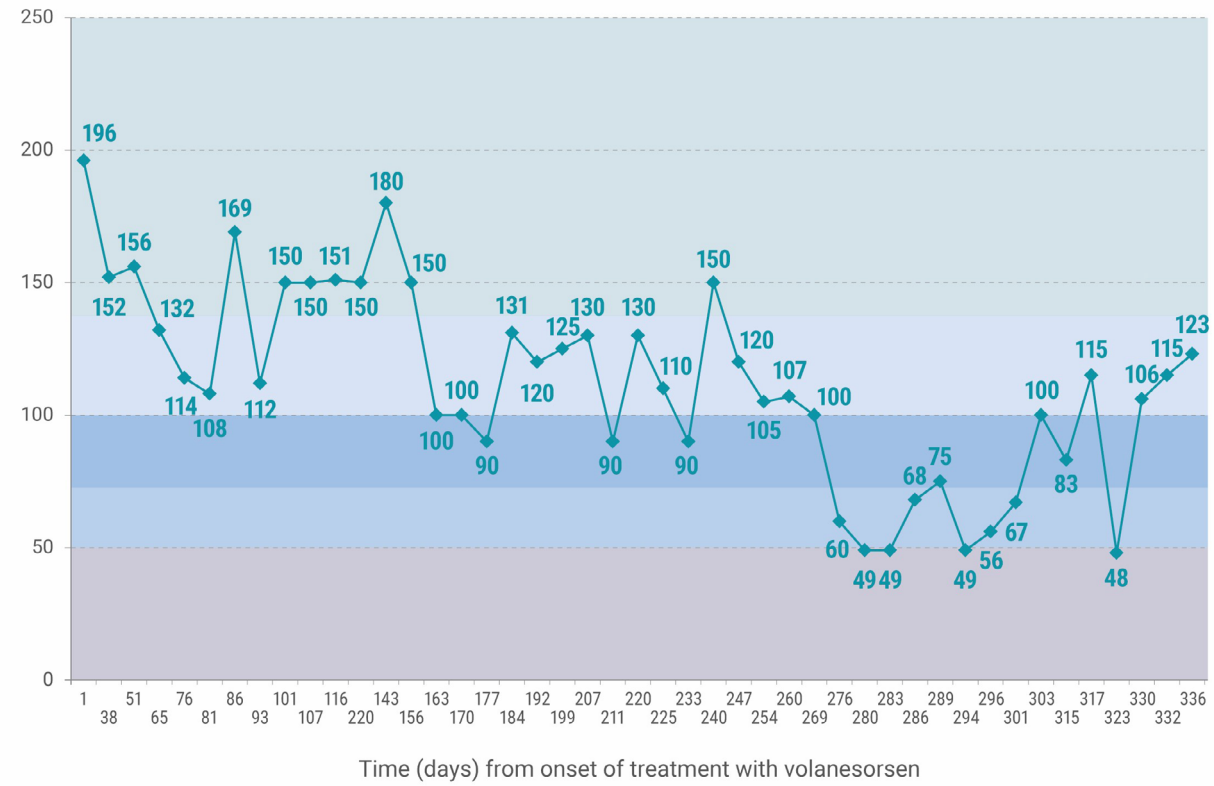

Figure 2. Platelet counts ($\times 10^9$/μL).

Treatment with volanesorsen was briefly discontinued due to elevated transaminases, which then returned to normal. During this time, a transient increase in TG levels was described (Figure 1). Treatment with volanesorsen is still ongoing, including safety follow-up visits.

Discussion

Recurrent acute pancreatitis is the leading cause for concern in patients with FCS; cognitive phenomena have also been described in the long term in association with hyperviscosity. The reported prevalence of acute pancreatitis among patients with FCS may be close to 67% and the rate of major complications, including death, is higher compared to patients with pancreatitis and without hypertriglyceridemia [6]. The risk of pancreatitis is expected to be reduced while TG levels remain below 750 mg/dL [6].

In our patient, NGS led to the detection of two heterozygous variants (c.984G>A and c.1139+6T>C) in the *LPL* gene. None of these variants had been previously reported in the main databases available [7,8,9] and their clinical implications may be uncertain. In contrast, the c.984G>A variant can be found in the critical functional α/β hydrolase domain and the evidence suggests that this mutation may have a detrimental impact [10]. Also, intronic variants similar to c.1139+6T>C have been linked to aberrant splicing based on computational models [11]. In a gene sequencing test performed in the patient's sister, an heterozygous variant c.1374>CA p-(Tyr458Ter) in *LMF1* gene was diagnosed, also related with a higher risk of FCS.

Hypertriglyceridemia was refractory to conventional therapy with fibrates and omega-3 fatty acids. Treatment with volanesorsen was initiated based on its currently approved indication as an adjunct to diet in adult patients with confirmed FCS and at high risk for pancreatitis, in whom response to diet and TG-lowering therapy has been inadequate [12]. This treatment strategy has proven to be effective and well-tolerated. It is worth noting that even though TG levels persisted above normal ranges, our patient has shown no abdominal symptoms or any other clinical manifestations during follow-up.

Even though we can not rule out that biliary stones may have triggered episodes of acute pancreatitis, it is important to underscore the role of hypertriglyceridemia as a strong risk factor for this complication. Most data on the pathophysiology of pancreatitis in this setting comes from animal models. TG are not inherently toxic to the pancreas, but free fatty acids originated from TG metabolism may induce lipotoxicity. The severity of pancreatitis may depend on the inflammatory response, resulting from local high levels of free fatty acids. Factors involved in TG-related pancreatitis included the release of intracellular calcium, increase of interleukins, ischemia secondary to releasing of vasoconstrictor molecules in pancreatic microcirculation, and acinar necrosis due to aggregation of free fatty acids into micelles with detergent-like properties [13].

It is worth mentioning that our patient had no additional risk factors for diabetes (family history, sedentarism, high body mass index, etc.), highlighting the impact of pancreatitis as the main probable etiology of this secondary metabolic disorder.

Volanesorsen is a second-generation chimeric antisense therapeutic oligonucleotide that selectively binds to apoC-III messenger ribonucleic acid (mRNA) within the 3′ untranslated region. This binding prevents translation and enables ribonuclease H1-mediated mRNA degradation, thereby promoting TG clearance through LPL-independent pathways [14]. APPROACH was a phase III, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of volanesorsen in 66 patients with FCS. Patients receiving volanesorsen showed a 77% decrease in mean fasting TG levels (defined as the primary endpoint), which was consistent with a mean reduction of 1712 mg/dL (95% confidence interval [95% CI]: 1330 to 2094 mg/dL), whereas patients receiving placebo had an 18% increase in mean plasma TG levels, representing an increase of 92 mg/dL [6]. In addition, the phase III trial COMPASS was an international, randomized, placebo-controlled, double-blind study that enrolled 114 patients with severe multifactorial hypertriglyceridemia or FCS, with fasting plasma TG levels ≥500 mg/dL. Subjects were randomized to treatment with volanesorsen (n = 76) or placebo (n = 38). Volanesorsen decreased mean plasma TG levels by 71.2% (95% CI: 63.2% to 79.3%) at 3 months from baseline, compared to 0.9% in the placebo arm, representing a mean absolute reduction of 869 mg/dL (95% CI: 720 to 1018 mg/dL) in the volanesorsen arm. Five events of acute pancreatitis were reported during the treatment period; all of these events occurred in three of the 38 patients in the placebo arm [15].

In terms of safety and tolerability, 75% of adverse events reported across clinical trials were mild in severity. The most common adverse reactions included abdominal pain, nasopharyngitis, fatigue and headache [14]. Thrombocytopenia has been reported in clinical trials and needs special consideration. However, the majority of platelet counts recovered following transient treatment discontinuation or changes of administration schedules [14]. In our patient, platelet counts were rapidly restored following a short cycle of corticosteroids. During follow-up, platelet counts were maintained in hemostatic ranges, without clinical significance.

Conclusion

We believe that a comprehensive approach capable of addressing the value of genetic characterization is essential, together with the burden of clinical events and the sum of all present factors. A mutation of unknown clinical significance may be certainly described in the context of a patient's full clinical picture (history, comorbidities, clinical stigmas and patient outcome during follow-up) and it is our opinion that these findings should guide treatment decisions.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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