

Significant Quality of Life Improvement Observed in a Patient With FCS Associated With a Marked Reduction in Triglycerides

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Familial chylomicronemia syndrome (FCS) is a rare genetic disorder characterized by severely high triglycerides (TGs). It is associated with a marked increase in risk of recurrent, potentially fatal acute pancreatitis (AP), and symptoms including abdominal pain, fatigue, and anxiety that may substantially reduce quality of life (QoL). A 46-year-old woman with FCS and severely high TGs initially presented with necrotizing pancreatitis with pseudocysts, having previously experienced recurrent AP. The patient reported constant abdominal pain and fatigue, which were evident in her demeanor. Initial management included maximum doses of omega-3 fatty acids and fibrates, plus an extremely restricted diet (reduced intake: calories, fats, simple sugars; no alcohol). Despite adherence to all management strategies, TGs remained at approximately 2800 mg/dL (31.6 mmol/L) and symptoms persisted. The patient was enrolled in COMPASS, a phase 3, placebo-controlled trial to evaluate the effect of an investigational drug, volanesorsen, on fasting TGs in patients with hypertriglyceridemia (fasting TGs ≥ 500 mg/dL [≥ 5.7 mmol/L]). The woman, a confirmed FCS patient, continued into the open-label extension study, during which fasting TGs decreased to 146 mg/dL (1.7 mmol/L) following 4 months of treatment. The restrictive diet was maintained throughout treatment and no serious adverse events were reported. Along with sustained TG reduction, the patient experienced progressive, perceived improvements in observable QoL measures and a marked reduction in symptom severity and frequency. In a patient with FCS, reduction in TGs following volanesorsen therapy appeared to be associated with marked improvement in clinical symptoms and observed QoL.

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Familial chylomicronemia syndrome (FCS) is a rare metabolic disorder characterized by severely high triglycerides (TGs) in the range of 1500 to 15 000 mg/dL (17-170 mmol/L) (1, 2). TG levels of 1000 mg/dL or greater (11.3 mmol/L or greater) are considered to be a strong risk factor for acute pancreatitis (AP) (3), and patients with FCS have a marked increase in risk of severe, recurrent, and potentially fatal AP (1, 4). In addition to AP, patients with FCS can present with a multitude of symptoms, including nausea, vomiting, eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, cognitive impairment, and recurrent episodes of mild to incapacitating abdominal pain that contribute to a high disease burden and diminished quality of life (QoL) (2, 5). Patients with FCS have their QoL affected in multiple areas that extend beyond the physical burden and are frequently not fully

Abbreviations: AP, acute pancreatitis; apoC-III, apolipoprotein C3; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; LPL, Lipoprotein Lipase; QoL, quality of life; TG/s, triglyceride/s.

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captured in standard evaluations such as the EQ-5D and the Short-Form 36 Health Survey. The IN-FOCUS study further elucidated the burden of FCS on patients and detailed the myriad impacts that the disease has on all aspects of their lives (1). The recognition and diagnosis of FCS patients can be challenging because of the heterogeneous manifestations (2). FCS is caused by mutations in the lipoprotein lipase (*LPL*) gene or, less frequently, in genes encoding proteins necessary for LPL function, including *APOC2*, *APOA5*, *LMF-1*, and *GPIHBP1* (1, 2, 6). LPL is a key enzyme in the catabolism of TG-rich lipoproteins following fat intake, in particular chylomicrons and very low-density lipoproteins (2).

The only currently available management option for patients with FCS is to follow an extremely restrictive, very low-fat diet (≤ 20 g/d), limit simple carbohydrates, abstain from alcohol, and avoid medications known to increase TG levels, such as thiazides, β -blockers, and exogenous estrogen (4, 5). Despite strict dietary adherence, TGs commonly remain high, resulting in patients remaining at risk of AP and continuing to experience distressing and debilitating symptoms (1, 4). We present a case of clinically improved symptom burden in a patient with FCS following substantial TG reduction, corresponding to notable improvement in observed QoL.

1. Case Report

A. Patient History

A 46-year-old woman of Southeast Asian origin was referred to the Polyclinic for Endocrinology, Diabetes and Preventive Medicine, University of Cologne, in 2012 after an episode of necrotizing pancreatitis with known pancreatic pseudocysts. Genetic analysis revealed LPL deficiency (compound heterozygote, with 2 mutations in the *LPL* gene c.209A>G and c.784C>T). The patient had been previously diagnosed with type 2 diabetes (controlled by diet) and high blood pressure. Extremely high TG levels (> 1000 mg/dL [11.3 mmol/L]) had previously been recorded, and the patient had experienced several episodes of AP requiring hospitalization.

A review of the patient's family history revealed hypertriglyceridemia (HTG) in both brothers (> 1000 mg/dL [11.3 mmol/L]), with one also having experienced multiple episodes of AP. No history of elevated TGs was reported on the maternal side; however, a history of cardiovascular events was recorded on the paternal side.

Management of the patient before referral included maximum doses of omega-3 fatty acids (Omacor 4000 mg daily; Pronova BioPharma) and fibrates (Lipidil ONE 145 mg; Mylan), plus a restricted diet consisting of reduced intake of calories, fats, simple sugars, and no alcohol. Despite adherence to all management strategies, TGs remained at approximately 2850 mg/dL (32.2 mmol/L) and symptoms persisted unchanged. It was noted that the patient had a gray complexion and reported constant abdominal pain and fatigue, which limited her daily activities. In addition to the patient's reported diminished QoL, family members also described experiencing constant worry and stress regarding her health.

B. Management and Outcome

In 2015, the patient was enrolled in COMPASS, a phase 3, placebo-controlled trial to evaluate the effect of an experimental drug, volanesorsen, on fasting TGs in patients with HTG (fasting TGs ≥ 500 mg/dL [5.7 mmol/L]) (7). Volanesorsen is a second-generation 2'-O-(2-methoxyethyl)-modified antisense inhibitor of apolipoprotein C3 (apoC-III) synthesis (6). On entry into the study, the patient's baseline fasting TGs were recorded at 2733 mg/dL (30.9 mmol/L). No impact on TG levels was reported in the initial double-blind period of the COMPASS study. Per protocol as a confirmed FCS patient, and following her consent, the patient continued into the open-label extension of the study, during which fasting TGs were observed to gradually decrease from 2851 mg/dL (32.2 mmol/L) to a low of 146 mg/dL (1.7 mmol/L) after 4 months of treatment (300 mg volanesorsen administered subcutaneously

1/wk). This corresponds to an absolute decrease of 2705 mg/dL (30.6 mmol/L) or a 94.8% decrease in TG levels in this patient. Fasting TG levels were measured monthly (Fig. 1). The restrictive diet was maintained by the patient throughout treatment, and no serious adverse events were reported. The patient tolerated the drug extremely well, had no treatment associated side effects, and never had a drop in her platelet count to less than 150 000. Along with sustained and substantial TG reduction, and an absence of further AP attacks, the patient described experiencing reductions in symptom severity and frequency and reported improvements in daily functioning and overall QoL. The patient initially reported substantially limiting travel over several years because of health concerns, but recently felt well enough to take a 4-week vacation. The patient described having a better outlook on life while on treatment, experiencing less fatigue and greater energy.

2. Discussion

Here, we report a case of a patient with FCS manifesting with severe HTG (refractory to diet and conventional lipid-lowering therapies) and severe ongoing abdominal pain, who was hospitalized multiple times with AP. The patient reported experiencing an extremely diminished QoL resulting from a combination of constant debilitating symptoms and fear of hospitalization. Patient family members also reported noticeable strain due to stress regarding the patient's health. The patient was examined by multiple physicians over several years before being diagnosed, highlighting the often convoluted route to diagnosis. The persistent symptoms, diminished QoL, and lengthy journey to diagnosis reported here were consistent with findings from the IN-FOCUS study, an online, anonymous quantitative research study designed to determine the extent of burden of disease on patients with FCS (1).

The impact of an extremely restrictive, very low-fat diet on TG levels of patients with FCS can be limited. As highlighted in this case, lipid-lowering agents such as fibrates, and omega-3 fatty acids are generally ineffective in patients with FCS, primarily because they act by enhancing LPL activity (8, 9). Following treatment with volanesorsen, the patient's TG levels decreased substantially and were maintained at a low level over a 6-month period. Volanesorsen inhibits the synthesis of apoC-III, a key regulator of plasma TG levels. The mode of action of apoC-III is postulated to be through inhibition of LPL activity (6). However, recent studies suggest that apoC-III also modulates TG levels through LPL-independent pathways, and therefore inhibition of apoC-III synthesis can be effective in reducing TG levels in patients with FCS. Reductions in TG levels in this case appeared to correspond to noted improvements in overall QoL, both physically and mentally. The reported QoL improvements extended beyond day-to-day functioning and even allowed for travel for the first time in several years.

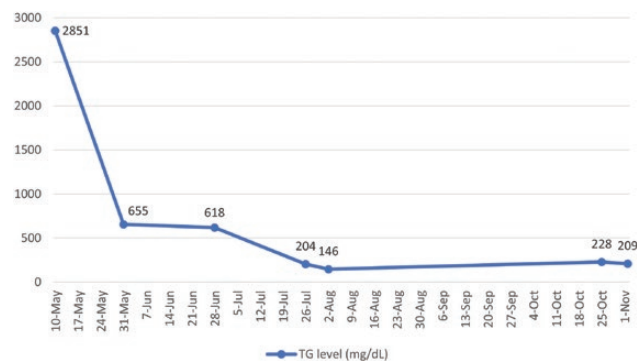


Figure 1. Patient fasting triglyceride (TG) levels. Measured patient TG levels during the open-label extension portion of the COMPASS study.

3. Conclusion

FCS is a rare, often underrecognized metabolic disorder that is characterized by severely high TG levels that are associated with diverse and serious clinical manifestations. FCS should be suspected in patients with severe HTG with no known secondary cause that is unresponsive to traditional lipid-lowering medications. Despite maintenance of a severely restricted diet, many patients still experience debilitating symptoms and remain at risk for AP. Substantial reduction in TGs with volanesorsen treatment appeared to be associated with noted improvements in clinical symptoms, as well as observed QoL, in a patient with FCS.

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Additional Information

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