Case Report

The Use of Orlistat in an Adult with Lipoprotein Lipase Deficiency: A Case Report

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A B S T R A C T

Background: Patients with lipoprotein lipase (LPL) deficiency, an inherited disorder, develop hypertriglyceridemia, which can lead to recurrent pancreatitis. The mainstay of therapy is medical nutritional therapy.

Case Report: We present the case of a 35-year-old woman with LPL deficiency who experienced recurrent hospitalizations for hypertriglyceridemia-induced pancreatitis, which was effectively treated with orlistat.

Discussion: Other agents that have been studied for the treatment of LPL deficiency are costly and have limiting side effects. Studies have shown orlistat to be safe and effective for the treatment of LPL deficiency in children. No studies have been performed in adults with LPL deficiency.

Conclusion: Orlistat may be a potential adjunctive treatment option for LPL deficiency in adults, given its availability and favorable safety profile. Further research regarding orlistat in the setting of LPL deficiency is needed.

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Introduction

Familial lipoprotein lipase (LPL) deficiency is an autosomal recessive disorder, with a prevalence of 1 in 1 000 000. The LPL enzyme is responsible for triglyceride lipolysis and peripheral free fatty acid uptake. When LPL is deficient, chylomicrons accumulate and cause significant hypertriglyceridemia. The diagnosis of LPL deficiency should be suspected when a patient <40 years of age presents with recurrent acute pancreatitis, eruptive cutaneous xanthomata, hepatosplenomegaly, milky-appearing plasma, and a plasma triglyceride level of >2000 mg/dL. The diagnosis is confirmed using molecular genetic testing. LPL deficiency is treated with medical nutrition therapy to maintain the triglyceride levels at <2000 mg/dL (ideally <1000 mg/dL). Patients are restricted to consuming <20 g of fat per day or 15% of the total energy intake.

However, when fat restriction is unsuccessful, there are few available treatment options. Studies in children have shown promise in terms of the use of orlistat, a gastric and pancreatic lipase inhibitor that can reduce fat absorption by up to 30%. However, there are no studies on orlistat use in adult patients with LPL deficiency. We present the first case of an adult with LPL deficiency who was started on orlistat therapy, which resulted in triglyceride levels of <1000 mg/dL.

Case Report

The patient, a 35-year-old woman, had a history of diabetes, hypercholesterolemia, and hypertriglyceridemia. Since the age of 12 years, she had been intermittently dependent on insulin, without a positive antibody test result or episodes of diabetic ketoacidosis, and was thought to have type 2 diabetes. Antibodies for glutamic acid decarboxylase, islet cell 512, and insulin were absent. C-peptide levels were detectable in the settings of euglycemia and hyperglycemia. Her triglyceride levels were consistently >1000 mg/dL despite adherence to a low-fat diet and treatment with a combination of icosapent ethyl, rosuvastatin, and fenofibrate. She denied any significant family history of hyperlipidemia.

Abbreviations: APOC3, apolipoprotein C-III; FCS, familial chylomicronemia syndrome; LPL, lipoprotein lipase.

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She reported having an episode of pancreatitis at the age of 29 years, which was believed to be secondary to sitagliptin. She was noted to have eruptive cutaneous xanthomata and hepatosplenomegaly.

Genetic testing revealed the presence of a heterogenous nonsense variant of LPL, ie, c.423G>A, p.(Trp141*), which was likely pathogenic. There was a premature stop codon at protein position 141, predicted to have caused the loss of normal function (protein truncation or nonsense-mediated messenger RNA decay); this has not been previously reported in the medical literature. This partial LPL deficiency confirmed the diagnosis of type 1 familial dyslipidemia in the patient.

Because of the persistent hypercholesterolemia, the patient was started on the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab in September 2017; however, her low-density lipoprotein levels remained >400 mg/dL and triglyceride levels >4000 mg/dL. She was subsequently hospitalized for acute pancreatitis in August 2018. She was treated with intravenous insulin, and at the time of discharge, she had a triglyceride level of 401 mg/dL. Upon discharge, evolocumab was discontinued and the patient’s home regimen of icosapent ethyl, rosvuastatin, and fenofibrate was continued. She was again hospitalized in November 2018 for recurrent acute pancreatitis, with triglyceride levels >3000 mg/dL. Intravenous insulin was initiated. She was started on orlistat, with an improvement in her triglyceride level to 798 mg/dL at discharge. Since the initiation of orlistat, the patient has not required any hospital admissions for acute pancreatitis and her triglyceride levels have remained <1000 mg/dL in the outpatient setting.

Discussion

Treatment options for LPL deficiency-induced hypertriglyceridemia are limited. Besides a low-fat diet, patients are counseled to avoid medications and other agents that increase triglyceride levels. Fish oil supplements are contraindicated because they increase chylomicron levels. In addition, statins have not been shown to be effective because they do not induce LPL activity. In 2013, 2 siblings with LPL deficiency (a 7-year-old girl and a 9-year-old boy with a history of recurrent pancreatitis) were treated with orlistat at the University of Oklahoma Health Sciences Center, leading to reduced levels of serum triglycerides and episodes of pancreatitis in the boy. In a 2018 study conducted at UT Southwestern Medical Center, 2 unrelated Asian Indian boys, aged 9 and 11 years, with type 1 hyperlipoproteinemia (homozygous large GPNBHP1 deletions) were randomized to receive 3 months of orlistat or no therapy and then crossed over to the other arm, after which this sequence was repeated. Treatment with orlistat reduced the serum triglyceride levels from 45.8% to 62.2%, with minimal adverse effects (increased bloating, flatulence, constipation, mild stool leakage). The study suggested that orlistat should be the first-line therapy in addition to a low-fat diet. Furthermore, a case report by Tzotzas et al. on orlistat use in a 34-year-old man with familial chylomicronemia demonstrated a reduction in the fasting serum triglyceride levels by 33% when 20 g of medium-chain triglycerides was consumed in addition to 50 g of other dietary fats.

The mechanism of hypertriglyceridemia leading to acute pancreatitis remains unclear. In a study by Wang et al., LPL-deficient mice with hypertriglyceridemia-induced pancreatitis had higher amylase levels and more-severe inflammation than wild-type mice. Additionally, treating isolated pancreatic acinar cells with free fatty acids and chylomicrons also led to increased amylase levels and inflammation. Furthermore, the effect of chylomicrons was partially blocked by orlistat. It appears that free fatty acids exert a toxic effect directly on pancreatic cells.

The other potential treatments include aliquote tiparovec, the first gene therapy for LPL deficiency, approved in Europe in 2012. The LPL gene is intramuscularly delivered via an adeno-associated viral vector 1, which leads to the expression of the naturally occurring p.S447* variant of the human LPL gene. Over 40 intra-muscular injections are given with the patient under spinal anesthesia. Although the serum triglyceride levels initially improve, patients eventually develop antibodies to the capsid proteins. The medication was withdrawn from the market in April 2017 because the average cost was approximately $1 million per treatment. Another potential therapy is lomitapide, which is an inhibitor of microsomal triglyceride transfer protein, resulting in the reduction of chylomicron and very low-density lipoprotein levels. A case report of a 44-year-old woman with LPL deficiency and recurrent pancreatitis showed that lomitapide reduced her triglyceride levels from 3000 mg/dL to a mean of 524 mg/dL. However, she developed medication-related hepatotoxicity and fibrosis in 12 to 13 years. Another alternative therapy that has been investigated in patients with LPL deficiency is apolipoprotein C-III (APOC3). APOC3 inhibits LPL, although it may elevate the plasma triglyceride levels via an LPL-independent mechanism. Treatment with an APOC3 messenger RNA inhibitor, called ISIS 304801, was initiated in 3 patients with familial chylomicronemia syndrome (FCS) and triglyceride levels ranging from 1406 to 2083 mg/dL (15.9 to 23.5 mmol/L). After 13 weeks of the administration of the study drug, the plasma APOC3 levels were reduced by 71% to 90% and triglyceride levels by 56% to 86%. During the study, all patients had a triglyceride level of <500 mg/dL (5.7 mmol/L) with the treatment. These data support the role of APOC3 as a key regulator of LPL-independent pathways of triglyceride metabolism. Additionally, ISIS 304801, also known as volanesorsen, has been studied in a randomized, double-blinded, placebo-controlled, phase 3 clinical trial (the APPROACH study) consisting of 66 patients with FCS with a mean baseline triglyceride level of 2209 mg/dL; the primary endpoint was triglyceride level reduction. The APPROACH study demonstrated that volanesorsen-treated patients had triglyceride level reductions of 53% at 6 months and 40% at 12 months. An adequate response was defined as a >40% reduction in triglyceride levels; 88% of the volanesorsen group achieved an adequate response, compared with 9% in the placebo arm (P < .0001). However, 5 patients in the volanesorsen arm experienced thrombocytopenia, of whom 2 patients had a platelet count of <24 000/µL, leading to early termination. Furthermore, volanesorsen has been approved for patients with LCS only in the European Union but has not been approved by the Food and Drug Administration. Despite multiple novel therapies investigated for triglyceride level reduction in patients with LPL deficiency, no low-cost, globally available therapies currently exist as an adjunct therapy to a fat-restricted diet.

Conclusion

Although LPL deficiency is a rare, inherited lipid disorder, complications such as recurrent acute pancreatitis can have a debilitating effect on the individual. Medical nutritional therapy with a fat-restricted diet remains the main therapy to prevent recurrent acute pancreatitis. However, when strict dietary adherence fails, there are no adjunct pharmaceutical options to lower triglyceride levels in patients with LPL deficiency that are both readily available and without major adverse effects. Despite strict adherence to a fat-restricted diet, our patient continued to have repeated episodes of acute pancreatitis. She was started on a trial of orlistat, which resulted in the maintenance of triglyceride levels at
<1000 mg/dL, without any recurrent episodes of acute pancreatitis. Orlistat may be a viable adjunct therapy for patients with LPL deficiency in whom a fat-restricted diet fails. More research is needed on the efficacy of triglyceride control with orlistat in patients with LPL deficiency.

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Disclosure
The authors have no multiplicity of interest to disclose. The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the Department of Defense, the U.S. Air Force, the U.S. Army, the U.S. Air Force Medical Department, the United States Air Force Office of the Surgeon General, the U.S. Army Office of the Surgeon General or the U.S. Government.

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