Severe Hypertriglyceridemia With Pancreatitis

Case Report/Case Series

Severe Hypertriglyceridemia With Pancreatitis
Thirteen Years' Treatment With Lomitapide

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IMPORTANCE Recurrent pancreatitis is a potentially fatal complication of severe hypertriglyceridemia. Genetic defects and lifestyle risk factors may render this condition unresponsive to current treatments.

OBSERVATIONS We report this first case of long-term management of intractable near-fatal recurrent pancreatitis secondary to severe hypertriglyceridemia by a novel use of lomitapide, an inhibitor of microsomal triglyceride transfer protein, recently approved for treatment of familial homozygous hypercholesterolemia. The patient had been hospitalized many times for pancreatitis since age 15 years. Her serum triglyceride level averaged 3900 mg/dL while she received therapy with approved lipid drugs. She is homozygous for a coding mutation (P234L) in lipoprotein lipase, leaving her unable to metabolize triglycerides in chylomicrons and very low density lipoproteins (VLDL). Lomitapide reduces the secretion of chylomicrons and VLDL. Lomitapide, which was started when she was 44 years old after near-fatal pancreatitis, lowered her fasting triglyceride level from greater than 3000 mg/dL to a mean (SD) of 903 (870) mg/dL while she received 30 mg/d and to 524 (265) mg/dL while she received 40 mg/d; eliminated chronic abdominal pain; and prevented pancreatitis. However, fatty liver, present before treatment, progressed to steatohepatitis and fibrosis after 12 to 13 years.

CONCLUSIONS AND RELEVANCE Lomitapide prevented pancreatitis in severe intractable hypertriglyceridemia but at a potential long-term cost of hepatotoxicity.

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Recurrent pancreatitis is a severe and potentially fatal complication of hypertriglyceridemia.[1-3] A triglyceride level greater than 2000 mg/dL is defined as "very severe hypertriglyceridemia"[4] because these levels can cause pancreatitis.[1-4] A fasting triglyceride level of 1000 to 2000 mg/dL is defined as "severe hypertriglyceridemia" and carries a risk of pancreatitis because after eating, triglyceride levels may rise above 2000 mg/dL. (To convert triglycerides to millimoles per liter, multiply by 0.0113.)

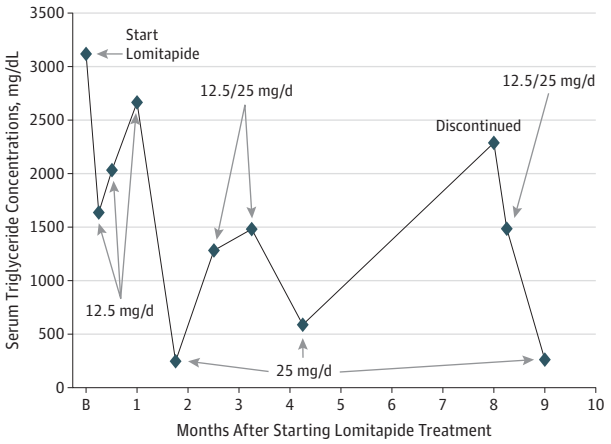
Severe and very severe hypertriglyceridemia can be caused by several genetic defects that impair metabolism by lipoprotein lipase of triglycerides in chylomicrons and very low density lipoproteins (VLDL).[5] This is also called familial chylomicronemia (type 1 dyslipidemia). Treatments that increase metabolism of triglycerides by lipoprotein lipase, such as fibrates or omega-3 fatty acids, are ineffective. Microsomal triglyceride transfer protein (MTP) transfers triglycerides and other lipids to apolipoprotein B48 in the enterocyte and apolipoprotein B100 in the hepatocyte, a necessary step to start the assembly of the lipid-protein complex in the enterocyte that will become a chylomicron or in the hepatocyte to become a VLDL or low-density lipoprotein (LDL).[6] Genetic deficiency of MTP causes abetalipoproteinemia, characterized by very low plasma levels of triglycerides.[6] Thus, MTP inhibitors could substantially lower plasma triglyceride levels by inhibiting the formation and secretion of triglyceride-rich lipoproteins.

Report of a Case

Clinical History Before Treatment With MTP Inhibition

The patient was first hospitalized for pancreatitis at age 15 years. She was treated with a low-fat diet; gemfibrozil, 1200 mg; omega-3 fatty acids; and niacin, singly or in combination; without benefit. She had had pancreatitis during each of her 3 pregnancies, at ages 23, 33, and 34 years, 1 of which ended in miscarriage. For the next 11 years, she experienced chronic abdominal pain, and recurrent pancreatitis requiring 12 hospitalizations, in spite of maximal dietary and drug treatment. The mean (SD) triglyceride level on hospital admission, not necessarily fasting, was 3570 (1619) mg/dL (median, 3179 mg/dL for 12 hospitalizations). During the last 1 to 2 years of this period, the patient's chronic abdominal

Figure 1. Serum Fasting Triglyceride Concentrations at Baseline (B) and During the First Year of Treatment With Lomitapide



The dose of lomitapide was adjusted to balance efficacy and tolerability. The patient's triglyceride level when receiving 12.5 mg/d averaged 2110 mg/dL, when receiving the alternating dose regimen of 12.5 mg/d and 25 mg/d averaged 1416 mg/dL, and when receiving 25 mg/d averaged 371 mg/dL. Discontinued indicates temporary cessation of lomitapide. (To convert triglycerides to millimoles per liter, multiply by 0.0113.)

pain worsened in intensity and duration, seriously damaging her ability to live normally. At age 44 years, she experienced a near-fatal episode of pancreatitis complicated by hypotension and acute respiratory distress syndrome that required intubation. A pancreatectomy was recommended as preventive treatment but was deferred to permit additional attempts at medical treatment. Three months later, pancreatitis returned, and she was admitted to the hospital with a serum triglyceride level of 4840 mg/dL.

Laboratory and Clinical Evaluations Before Treatment With Lomitapide

The patient's fasting serum triglyceride levels were usually higher than 2000 mg/dL. Her plasma was grossly lipemic. Additional findings were lipemia retinalis, anemia (hematocrit, 26%-34%), thrombocytopenia (platelet count, 100 000 cells/μL), and leucopenia (white blood cell count, 2000-4000/μL). A bone marrow biopsy specimen taken at age 31 years showed 40% replacement with macrophage-foam cells. Abdominal ultrasonographic findings repeatedly showed fatty liver and splenomegaly. Computed tomographic (CT) scans showed no hepatomegaly or other liver abnormality. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were usually within reference range. The patient did not have diabetes mellitus; her body weight was normal, with a body mass index, calculated as weight in kilograms divided by height in meters squared, of 21 to 22; and results from thyroid and renal tests were normal. She rarely drank alcoholic beverages. (To convert hematocrit to a proportion of 1, multiply by 0.01; to convert platelets to $\times 10^9$/μL, multiply by 1.0; to convert white blood cell count to $\times 10^9$/μL, multiply by 0.001.)

Genetic and Phenotypic Diagnosis

Direct sequencing of the patient's genomic DNA revealed homozygosity for the coding missense mutation (P234L) in the *LPL* gene producing noncatalytically active lipoprotein lipase (LpL).[7] The *LPL* P234L mutation has been found in Chinese persons in China[8] and in French Canadians.[7] The patient's ethnicity is Chinese. No other potential culprit mutations were found in coding regions, intron-exon boundaries and promoters of *APOC2*, *APOA5*, *LMF1*, and *GPIHBP1* genes.

Her plasma LpL mass concentrations were elevated (monomers, 1010 ng/mL [reference range, 150-300 ng/mL]; and dimers, 150 ng/mL [reference range, 50-100 ng/mL]),[9] consistent with the diagnosis of functionally defective LpL. The plasma apolipoprotein CII concentration was approximately 10 times the reference range (35 mg/dL [reference range, 1.6-4.2 mg/dL]).

The patient's mean serum fasting lipid levels just prior to lomitapide treatment were as follows: triglyceride level, 3109 mg/dL; LDL cholesterol (LDL-C) level, 63 mg/dL; high-density lipoprotein cholesterol (HDL-C) level, 29 mg/dL; and apolipoprotein B level, 745 mg/dL (reference range, <120 mg/dL). Apolipoprotein B100 and B48 levels were both elevated. (To convert LDL-C and HDL-C to millimoles per liter, multiply by 0,0259; to convert apolioprotein to grams per liter, multiply by 0.01.)

One of the patient's brothers also has severe hypertriglyceridemia and recurrent pancreatitis. Five other siblings have moderate hypertriglyceridemia but without pancreatitis, suggesting that at least some of them may be heterozygous for the *LPL* P234L mutation. Her parents' lipid levels are unknown.

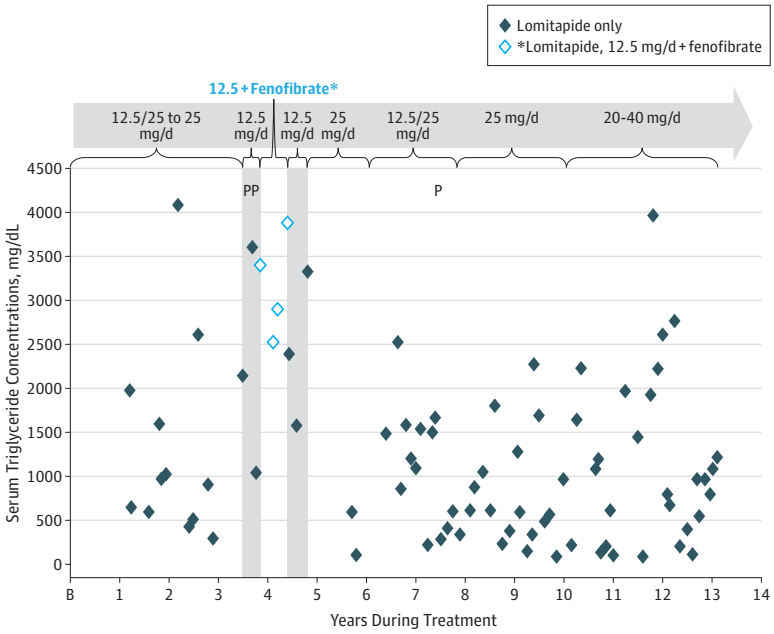
Treatment With MTP Inhibition

An emergency investigational new drug use and institutional review board approval for lomitapide were granted. Written informed consent was received. On June 7, 1999, other lipid-lowering therapy was stopped, and treatment was initiated with lomitapide, which was the first use of an MTP inhibitor for hypertriglyceridemia.

The lomitapide dose was titrated to balance the triglyceride-lowering effect with avoidance of diarrhea presumably caused by fat malabsorption (**Figure 1**). During the first year of treatment, the patient's fasting triglyceride level while receiving the 12.5 mg/d dose averaged 2110 mg/dL; while receiving the alternating 12.5 mg/d and 25 mg/d dose regimen, 1416 mg/dL; and while receiving the 25 mg/d dose, 371 mg/dL (Figure 1). A 6-month trial of adding fenofibrate, 200 mg/d, to lomitapide, 12.5 mg/d, in an attempt to control the hypertriglyceridemia with a lower dose of lomitapide was a failure (**Figure 2**). In 2009, Aegerion reformulated lomitapide into 20-mg and 40-mg capsules. The patient's fasting triglyceride levels during treatment with the 20 mg/d dose averaged 1604 mg/dL; during treatment with alternating 20 mg/d and 40 mg/d dose regimen, 903 mg/dL; and during treatment with 40 mg/d dose, 524 mg/dL (Figure 2). Her hematocrit level range increased from a range of 26% to 34% to a range of 38% to 40% after the fifth year.

To date, the patient has been treated with lomitapide for 13 years. She has had 3 brief uncomplicated hospitalizations

Figure 2. Serum Fasting Triglyceride (TG) Concentrations During Years 2 to 13 of Treatment With Lomitapide



Each episode of pancreatitis (P) is defined as brief uncomplicated hospitalization associated with not taking the drug or exceptionally high dietary fat intake (The 2 P's close to each other are simply 2 pancreatitis episodes that occurred at the times indicated on the x-axis). At year 4, a 6-month trial of adding fenofibrate, 200 mg/d, to lomitapide, 12.5 mg/d, to try to control the hypertriglyceridemia on a lower dose of lomitapide was a failure. The patient's mean serum TG level was 3175 mg/dL (range, 2525-3880 mg/dL; N = 4 TG tests) with the combination, compared with 2345 mg/dL (range, 1041-3600 mg/dL; N = 6 TG measurements) during treatment with lomitapide, 12.5 mg/d. This time period is indicated by vertical gray columns. In the 10th year, lomitapide was reformulated into 20- and 40-mg capsules. The mean (SD) TG levels during treatment with 20 mg/d was 1604 (1030) mg/dL (median, 1331 mg/dL; N = 13 TG measurements); during treatment with the alternating dose of 20 mg/d and 40 mg/d, 903 (870) mg/dL (median, 703 mg/dL; N = 10 TG measurements); and during treatment with the 40-mg/d dose, 524 (265) mg/dL (median, 542 mg/dL; N = 4 TG measurements). B indicates baseline. (To convert TG to millimoles per liter, multiply by 0.0113.)

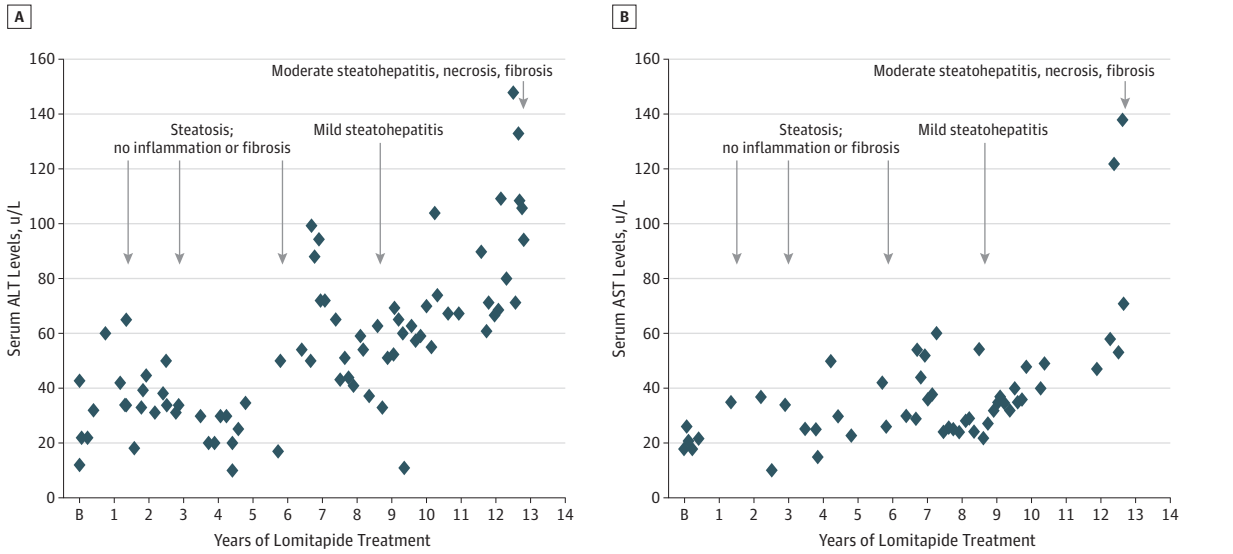
for pancreatitis during the third, fourth, and seventh years of treatment associated with either having no lomitapide or high dietary fat intake during visits to her family in China.

Hepatic Toxicity of Lomitapide

The patient's serum ALT and AST levels during the initial 6 to 7 years of lomitapide treatment were usually within reference range, increasing thereafter (**Figure 3**). Her alkaline phosphatase levels were within reference range before treatment and through 12 years of lomitapide treatment. In the 13th year, the alkaline phosphatase level increased to 130 and 143 U (upper limit of reference range, 125 U) (to convert alkaline phosphatase to microkatals per liter, multiply by 0.0167). Her serum bilirubin and albumin levels were within reference range before and during lomitapide treatment. Ultrasonographic examinations showed fatty liver, and findings from hepatic CT and magnetic resonance image scans were normal. Results of a liver biopsy at 1 year showed marked steatosis without necrosis, inflammation, fibrosis, or stainable iron; at 3 years showed severe microvesicular and macrovesicular steatosis, minimal lobular inflammation, mild cholestasis, without necrosis, fibrosis, or stainable iron; at 5 years showed marked predominantly macrovesicular steatosis without inflammation or fibrosis, and trace amounts of stainable iron; and at 8.5 years showed marked predominantly macrovesicular steatosis and mild steatohepatitis but no clinically significant fibrosis or stainable iron. The results from the most recent biopsy at 13 years showed severe mixed large- and small-droplet steatosis involving more than 66% of the core biopsy (NASH activity score, 3); frequent ballooning degeneration (score, 2); mild portal and septal and mild to focally moderate lobular mixed inflammation (score, 2); and portal, septal, and sinusoidal fibrosis (at least stage 3 fibrosis, focally early stage 3-4); and negative results from an iron stain.

Progression of fatty liver to hepatitis and fibrosis presents a therapeutic dilemma.[10] In lipoprotein lipase deficiency, large nascent triglyceride-rich chylomicrons and VLDL cannot be metabolized to smaller lipoproteins that can pass through the sinusoidal endothelial cell fenestrations to the hepatocytes that clear them from the circulation.[11] Instead, these large lipoproteins are taken up by the reticuloendothelial system in the liver, spleen, and bone marrow. Prior to lomitapide treatment, the patient did not have an increased serum transaminase level or hepatomegaly. The fatty liver repeatedly found on ultrasonography could have represented lipid-laden sinusoidal macrophages (Kupfer cells), suggested by their prevalence in the bone marrow. A liver biopsy was not performed before lomitapide treatment. In contrast, inhibition of hepatic MTP decreases a principal means that hepatocytes use to reduce their fat content.[12] The MTP inhibition in hypercho-

Figure 3. Serum Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) at Baseline and During 13 Years' Treatment With Lomitapide



The upper limits of normal were 40 U/L for ALT (A) and 35 U/L for AST (B). Findings of the liver biopsy described in more detail in the subsection titled "Hepatic Toxicity of Lomitapide." B indicates baseline. (To convert ALT and AST to microkatals per liter, multiply by 0.0167.)

lesterolemia increases liver transaminases and hepatic fat content.[13,14] Therefore, the hepatic pathophysiologic characteristics of lomitapide toxicity differ from those of lipoprotein lipase deficiency, and it is possible that the 2 separate effects may adversely interact. No other patient has been treated with lomitapide for more than 5 years, and thus the long-term effects of the drug in lipoprotein lipase deficiency as well as in familial hypercholesterolemia need to be studied carefully.

Discussion

Now that lomitapide is available in the United States for treatment of familial homozygous hypercholesterolemia, physicians may consider it to treat pancreatitis caused by severe hypertriglyceridemia. However, lomitapide is not approved for this "off-label" use, and it may be available only on a named patient compassionate use basis with approval of the manufacturer and the relevant health authorities and ethics committees. We suggest these criteria: (1) pancreatitis associated with severe hypertriglyceridemia, (2) failure of intensive diet and drug treatment to prevent episodes of pancreatitis, and (3) no active hepatitis or hepatic fibrosis.

We do not recommend using lomitapide in patients who have severe hypertriglyceridemia without pancreatitis because many of them never develop pancreatitis. A recent clinical case series reported that 16% of patients who had triglyceride levels higher than 1772 mg/dL had pancreatitis.[15] Maximum efforts to encourage dietary adherence must be made, especially because dietary fat will make the lomitapide less effective at a given dose and more prone to cause diarrhea. We emphasize that we used lomitapide in a desperate clinical situation in which the patient at any time could have a fatal attack of pancreatitis. If physicians choose to use lomitapide in such patients, they must report their results so experience will accumulate to understand the benefits and long-term risks.

ARTICLE INFORMATION

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Author Contributions: Dr Sacks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sacks.
Acquisition of data: Sacks, Stanesa, Hegele.
Analysis and interpretation of data: Sacks, Stanesa, Hegele.
Drafting of the manuscript: Sacks.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Sacks, Stanesa.
Administrative, technical, or material support: Hegele, Stanesa.
Study supervision: Sacks.

Conflict of Interest Disclosures: Dr Sacks has consulted for companies that develop or market drugs for dyslipidemia (Merck, ISIS, Genzyme, Sanofi, Lilly, Roche), given lectures (AstraZeneca) and was an expert witness (Abbott). Dr Hegele is a consultant and speaker for Abbott, Merck, Amgen, Valeant Pharma, Tribute Pharma, and Sunovion and was a consultant for Aegerion Pharmaceuticals. No other disclosures are reported.

Additional Information: Dr Sacks treated the patient and obtained the investigational drug. Ms Stanesa has been the patient's primary care provider during the duration of treatment. Dr Hegele directed the genotyping investigation.

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