Balancing Low-density Lipoprotein Cholesterol Reduction and Hepatotoxicity With Lomitapide Mesylate and Mipomersen in Patients With Homozygous Familial Hypercholesterolemia

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Homozygous familial hypercholesterolemia (HoFH) is an autosomal codominant disorder manifested by high concentrations of total cholesterol and low-density lipoprotein (LDL) cholesterol, and premature cardiovascular disease. Despite conventional lipid-lowering therapy, LDL cholesterol levels remain elevated in patients with HoFH; these patients are considered to be at high risk for cardiovascular events. In 2012-2013, two drugs with novel mechanisms of action were approved by the US Food and Drug Administration for the treatment of HoFH: lomitapide mesylate and mipomersen. Both of these treatments reduce total cholesterol, LDL cholesterol, non–high-density lipoprotein cholesterol, apolipoprotein B, lipoprotein a, and triglyceride levels. This review describes the clinical tradeoffs in efficacy and hepatotoxicity of these drugs in two cases of HoFH.

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KEY WORDS

Apolipoprotein B synthesis inhibitor • Familial hypercholesterolemia • Hepatotoxicity • Lomitapide mesylate • Mipomersen • Microsomal triglyceride transfer protein inhibitor

Homozygous familial hypercholesterolemia (HoFH) is characterized by very high total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations, which are strongly associated with premature coronary and systemic atherosclerosis, myocardial infarction, aortic stenosis, and cardiovascular death. Untreated patients rarely survive beyond the age of 30 years.[1,2] Mutations in alleles, coding for LDL receptors (85%-90% of cases), apolipoprotein B (apo B)-100 (5%-10% of cases), and proprotein convertase subtilisin kexin type 9 (PCSK9) (~1% of cases) create the phenotype of HoFH through very different pathophysiologic mechanisms.[2] Although true single-mutation homozygotes are identified in some founder populations, it is becoming increasingly recognized that compound heterozygotes (two or more different mutations on one or two alleles) or double heterozygotes (two or more mutations in the LDL receptor and/or apo B-100 and/or PCSK9) are responsible for the wide spectrum of lipid values and clinical manifestations of HoFH. Early initial treatment is essential because HoFH patients are exposed to high concentrations of LDL cholesterol over long periods, which is the basis for the pathophysiologic mechanism of severe premature atherosclerosis. Unfortunately, in most genotypes and phenotypes of HoFH, there is a modest response to statin drugs with a $<$ 50% reduction in LDL cholesterol level.[3] Patients who are statin intolerant are particularly worrisome because alternative agents, including bile acid sequestrants, ezetimibe, and nicotinic acid, have very modest treatment effects with symptomatic side effects.

In December 2012, the US Food and Drug Administration approved lomitapide mesylate (a microsomal triglyceride transfer protein inhibitor), and, in January 2013, approved mipomersen (an apo B synthesis inhibitor). Both agents underwent clinical development and market entry according to the US Orphan Drug Act of 1983.[3] Herein, we present two cases of HoFH to highlight the clinical tradeoffs with each agent and to shed light on the hepatotoxicity potential of both drugs.

Case 1

A 60-year-old white woman with severe coronary atherosclerosis presented for consultation and management of her hyperlipidemia. Her past medical history included percutaneous coronary interventions at age 44 and 45, followed by a three-vessel coronary artery bypass surgery at age 45. She later had a myocardial infarction at age 55 and has had stable class 3 angina with use of sublingual nitroglycerin spray for episodes of shortness of breath with chest and jaw discomfort. She reported complete intolerance to treatment with statin drugs due to myalgia in the past, which included attempts at rechallenge and alternative dosing regimens. With regard to family history, her mother had a total cholesterol level of $>$ 800 mg/dL and died at age 54 of coronary disease. Her sister was treated with lomitapide mesylate for a diagnosis of HoFH. One of her four children had heterozygous FH (HeFH). Initial vital signs included a blood pressure of 114/69 mm Hg, a pulse of 70 beats/min, and a respiratory rate of 16 breaths/min. She had xanthelasma in the periorbital areas, hard exudates on retinal examination, a grade 2/6 systolic ejection murmur over the aortic valve area consistent with aortic sclerosis, and soft bilateral carotid bruits. Peripheral pulses were normal. There were tendon xanthomas on the inner aspects of both Achilles tendons.

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Her initial cholesterol treatment began at age 30 with oral atorvastatin, 10 mg/d for 1 year, which continued with an elevated dosage of 80 mg/d by mouth for 15 years. The patient claimed that atorvastatin weakened her muscles, so it was replaced with simvastatin, which also caused myalgia at the lowest dose. She was then prescribed oral ezetimibe, 10 mg/d, for the past 4 years as her only lipid-lowering medication. Her other medications include oral aspirin, 81 mg/d, oral clopidogrel, 75 mg/d, oral metoprolol tartrate, 25 mg/d, and oral ranolazine, 1000 mg/d.

The baseline laboratory data demonstrated an LDL cholesterol level of 314 mg/dL and an aspartate aminotransferase (AST) level of 14 U/L (Figure 1). Oral lomitapide mesylate, 5 mg/d, was started, but the medical regimen was otherwise unchanged. At the 3-month follow-up visit, her LDL cholesterol level was reduced to 79 mg/dL, which was a 74.8% reduction. Although the LDL cholesterol level was lowered, hepatic transaminases began to elevate. The AST and alanine aminotransferase (ALT) levels rose to 135 U/L, and 169 U/L, respectively. At the 11th week of treatment, the dose was titrated up to 10 mg/d by mouth. After 6 months of treatment, the dose was titrated up to 20 mg/d by mouth, and her LDL cholesterol level was reduced

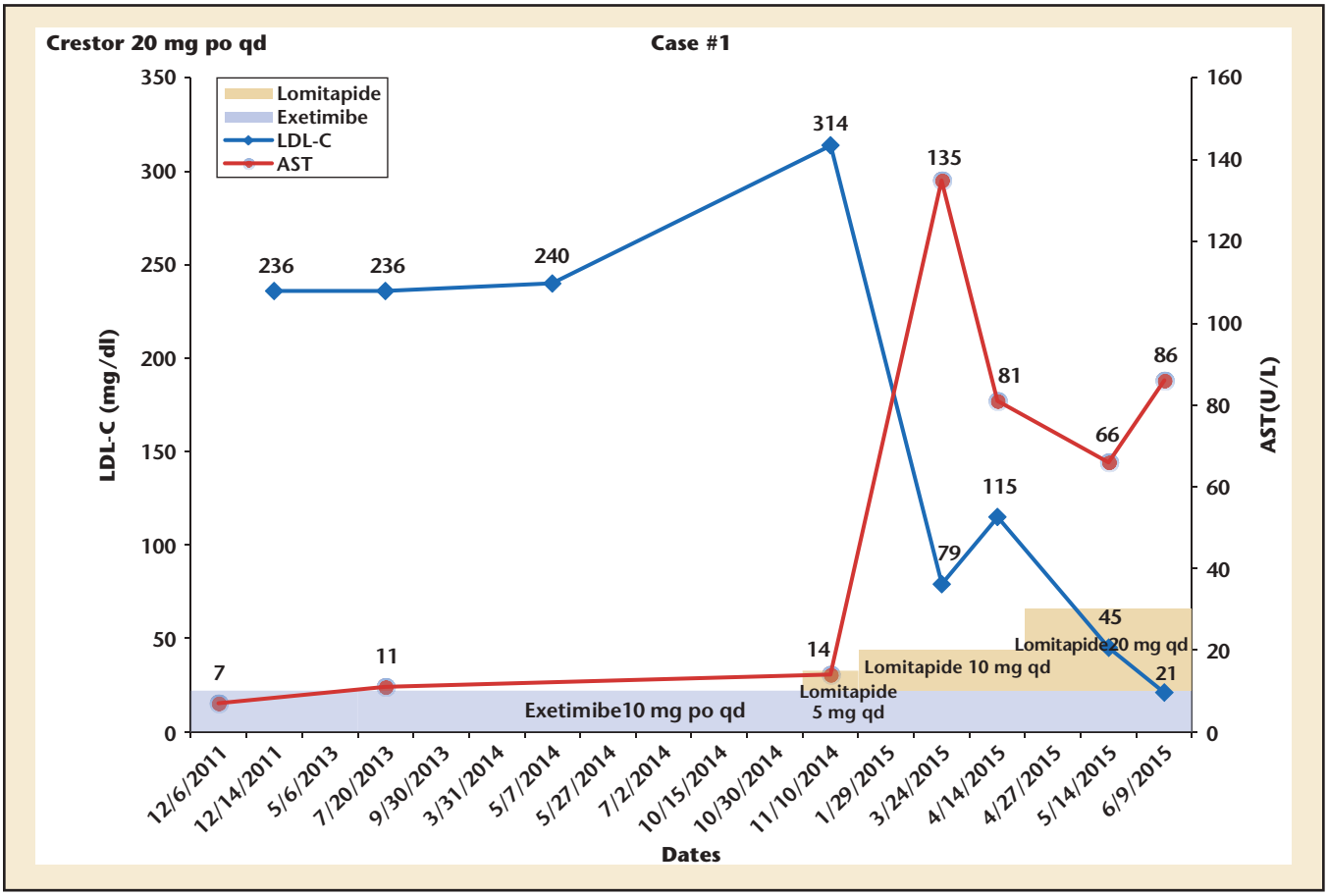

Figure 1. Relationship between LDL-C and aspartate aminotransferase in a patient treated with lomitapide and background lipid-lowering therapy for homozygous familial hyper-cholesterolemia over the course of 30 weeks. AST, aspartate aminotransferase; LDL-C, low-density lipoprotein cholesterol; po, by mouth; qd, once daily.

to 45 mg/dL (representing an 85.7% reduction from baseline). With continued lomitapide mesylate, 20 mg/d over 30 weeks of treatment, her LDL cholesterol concentration was reduced to 21 mg/dL and her total cholesterol decreased to 60 mg/dL. On one occasion, the patient complained of abdominal cramping and diarrhea, which was associated with alcohol and saturated fat intake. These symptoms resolved with changes in dietary intake.

Case 2

A 63-year-old nonsmoking black woman was evaluated for dyslipidemia; she had a medical history of morbid obesity, gastroesophageal reflux disease, and hysterectomy. She had gastric sleeve surgery at age 62, which resulted in weight loss, but no improvement in her dyslipidemia. Despite her adhering to a low-cholesterol diet after surgery, the patient's LDL cholesterol level remained > 300 mg/dL, and was only partially responsive to rosuvastatin. She complained of eye and mouth dryness, both of which had persisted for over 1 year. She denied having cardiovascular disease, but was diagnosed with a heart murmur 4 years ago. With regard to family history, she reported that her father died at age 80 years from a myocardial infarction, her mother had congestive heart failure, and her half-brother had elevated cholesterol values consistent with HoFH. She was a homemaker and consumed approximately eight alcoholic drinks per week.

Her medications included oral esomeprazole, 40 mg/d, oral sertraline, 50 mg/d, and oral trazodone, 50 mg/d, for the past 2 years, as well as rosuvastatin, 20 mg, for the past 5 years. The patient presented with a body mass index of 35.4 kg/m^2, blood pressure of 146/76 mm Hg, a pulse of 94 beats/min, and a respiratory rate of 16 breaths/min. Her physical examination was notable for xanthelasma in the periorbital region but was otherwise unremarkable. No tendon xanthomas were present. Laboratory diagnostic tests revealed a total cholesterol level of 322 mg/dL, a high-density lipoprotein cholesterol level of 69 mg/dL, and an LDL cholesterol level of 228 mg/dL.

She was started on mipomersen, 200 mg/mL, via subcutaneous injection once per week, and continued the rosuvastatin use. After 9 weeks, her LDL cholesterol level decreased to 109 mg/mL, representing a 52.2% reduction. At week

20, her LDL cholesterol declined to 47 mg/dL, a 79.4% reduction from baseline. Her AST level rose from 29 U/L at baseline to 112 U/L at week 22, a 286.2% increase (Figure 2). Mipomersen was continued and achieved a gradual reduction in hepatic transaminases with a sustained reduction at 34 U/L. The patient reported an injection site skin lesion and flu-like symptoms, which is a frequent side effect of the drug. No other adverse reactions or symptoms were reported.

Discussion

Our cases demonstrate that both lomitapide mesylate and mipomersen can lower LDL cholesterol levels considerably by impairing very different mechanisms: inhibiting the microsomal transferase protein (lomitapide mesylate) or by attenuating the production of apo B with antisense RNA therapy (mipomersen). In both cases, the use of concomitant medications, ezetimibe, and rosuvastatin provided a modest impact on LDL cholesterol levels; thus, these medications were continued with the novel therapies added to the medical regimen. We observed considerable hepatotoxicity in each case, which was temporally associated with LDL cholesterol reduction (Figures 1 and 2).

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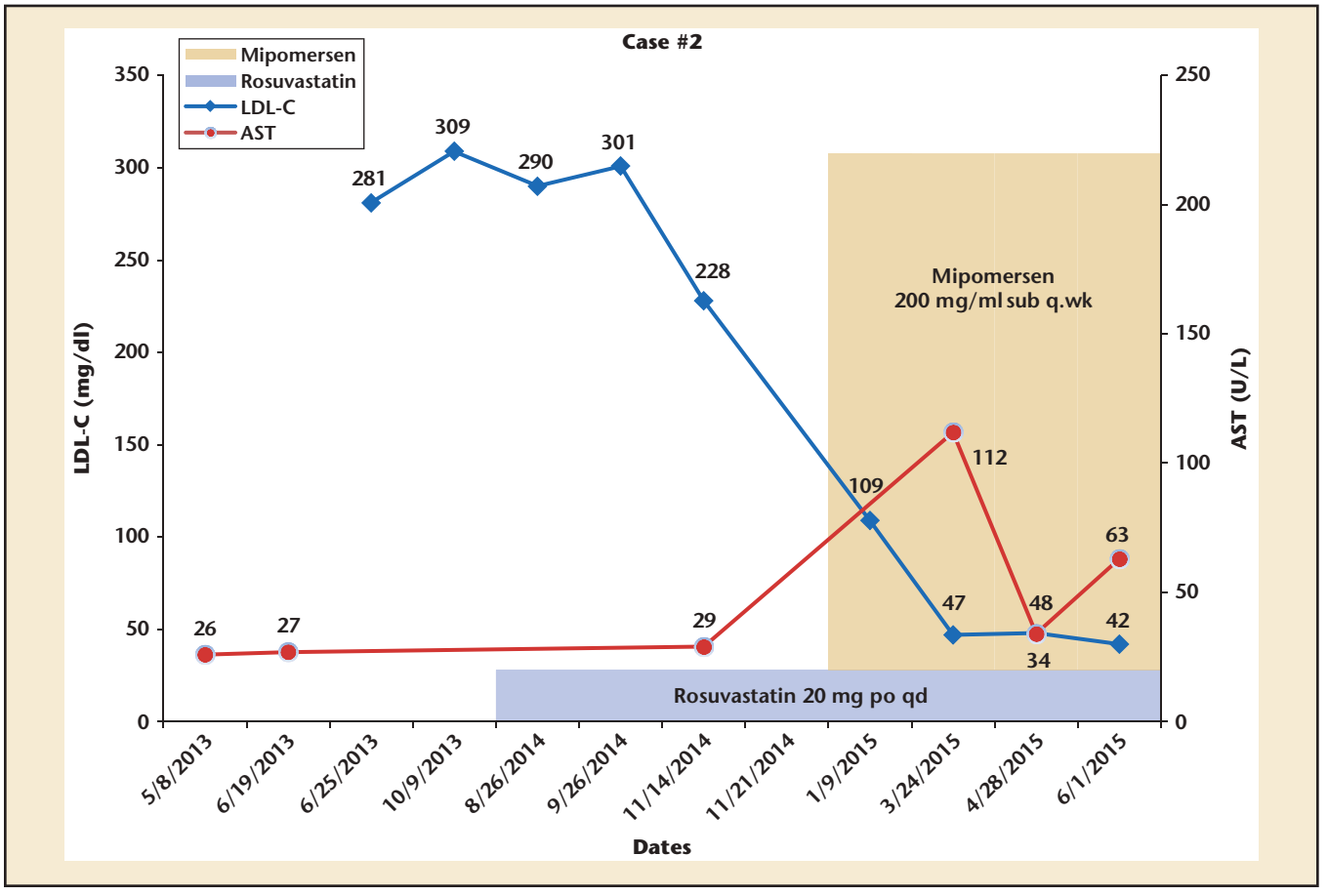
Familial hypercholesterolemia is an autosomal codominant disease caused by mutations in the LDL receptor gene (85%-90% of cases), *APOB* gene (5%-10% of cases), or the *PCSK9* gene (~1% of cases).[4] These three very different pathogenetic mechanisms and genotypes result in a common phenotype of familial hypercholesterolemia. Although some studies suggest that true HoFH is common with the same mutation on each allele in founder populations, other studies suggest that in mixed populations, that phenotype of HoFH results from compound heterozygotes (one or more different mutations at each allele) or double heterozygotes (mutations in the LDL receptor gene plus mutations in *APOB* or *PCSK9*). Unfortunately, commercial genetic testing can evaluate only a fraction of the > 1600 different familial hypercholesterolemia mutations known; therefore,

Figure 2. Relationship between LDL-C and aspartate aminotransferase in a patient treated with mipomersen and background lipid-lowering therapy for HoFH over the course of 20 weeks. AST, aspartate aminotransferase; LDL-C, low-density lipoprotein cholesterol; po, by mouth; qd, once daily; sub, subcutaneous.



the determination of HoFH must be made on clinical grounds. As genetic testing becomes more comprehensive, one can envision an approach where lomitapide or mipomersen is combined with monoclonal antibodies against *PCSK9* (alirocumab, evolocumab) for LDL receptor and *PCSK9* mutations, whereas mipomersen alone may be reasonable for patients with *APOB* mutations.

The US Orphan Drug Act of 1983 made it possible for lomitapide and mipomersen to be developed and commercially available in the United States (Table 1). These drugs are expensive: the cost of lomitapide mesylate ranges from $235,000 to $295,000 for annual treatments; mipomersen costs approximately $176,000 annually; and the recently approved anti-*PCSK9* monoclonal antibody, alirocumab, costs $14,600 annually.[4,5] In comparison with the statin treatment's yearly cost of $48 to $500, these drugs are drastically more expensive; however, statin drugs are often only modestly effective in HoFH and these costs must be weighed against the estimated costs for an HoFH patient who has a myocardial infarction or requires revascularization, which range from $50,000 to $119,000 for 1 year.[5]

Figure 3 demonstrates our first case in which consistent daily oral consumption of lomitapide mesylate in escalating doses resulted in a 93.3% reduction in LDL cholesterol levels from the baseline value over a 30-week follow-up.[2,4,6] Our patient could be considered a hyperresponder to lomitapide mesylate possibly due to concomitant use of ezetimibe and impairment in both cholesterol and fat absorption in the gastrointestinal tract. In our second case, metabolism can be demonstrated in Figure 4. Weekly subcutaneous injections of 200 mg/mL of mipomersen, which binds to the messenger RNA of apo B and deactivates ribonuclease H1, preventing translation of the messenger RNA and synthesis of apo B, reduced LDL cholesterol level significantly by 81.6% at week 31 from baseline.[7] This patient could also have been considered a hyperresponder to mipomersen, possibly due to impaired fat absorption

Figure 3. Triglyceride-rich lipoprotein metabolism. Shaded molecules (*purple*) are implicated in monogenic chylomicronemia. *Dashed lines* indicate a key functional role of the apolipoprotein in lipolysis. In healthy individuals, dietary fat is hydrolyzed by pancreatic lipase and requires emulsification with bile salts, which are produced by the gallbladder. FFA enter intestinal cells via FABP. Triglyceride-rich lipoproteins of intestinal origin are assembled in a multistep process requiring DGAT and MTTP, and enter the circulation (through the lymphatics) as chylomicrons, which are composed of ~90% triglycerides with a small amount (1%-3%) of cholesterol ester and are surrounded by a phospholipid envelope containing several apolipoprotein molecules, including the chylomicron-specific apoB-48, as well as apoA-I, apoA-V, apoC-II, apoC-III and apoE. In contrast, endogenously derived triglyceride-rich lipoproteins of hepatic origin are assembled de novo in a process requiring MTTP and DGAT; these lipoproteins circulate in plasma within apoB-100-containing VLDL particles. A-I, apolipoprotein A-I; A-IV, apolipoprotein A-IV; A-V, apolipoprotein A-V; B-48, apolipoprotein B-48; B-100, apolipoprotein B-100; C-II, apolipoprotein C-II; C-III, apolipoprotein C-III; CM, chylomicron; CMR, chylomicron remnant; DGAT, diacylglycerol O-acyltransferase; E, apolipoprotein E; FABP, fatty acid-binding protein; FAS, fatty acid synthase; FFA, free fatty acid; GPI-HBP1, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1; IDL, intermediate density lipoprotein; LRP1, LDL receptor-related protein 1; LMF1, lipase maturation factor 1; LPL, lipoprotein lipase; MTTP, microsomal triglyceride transfer protein. Reprinted with permission from Brahm and Hegele.[6]

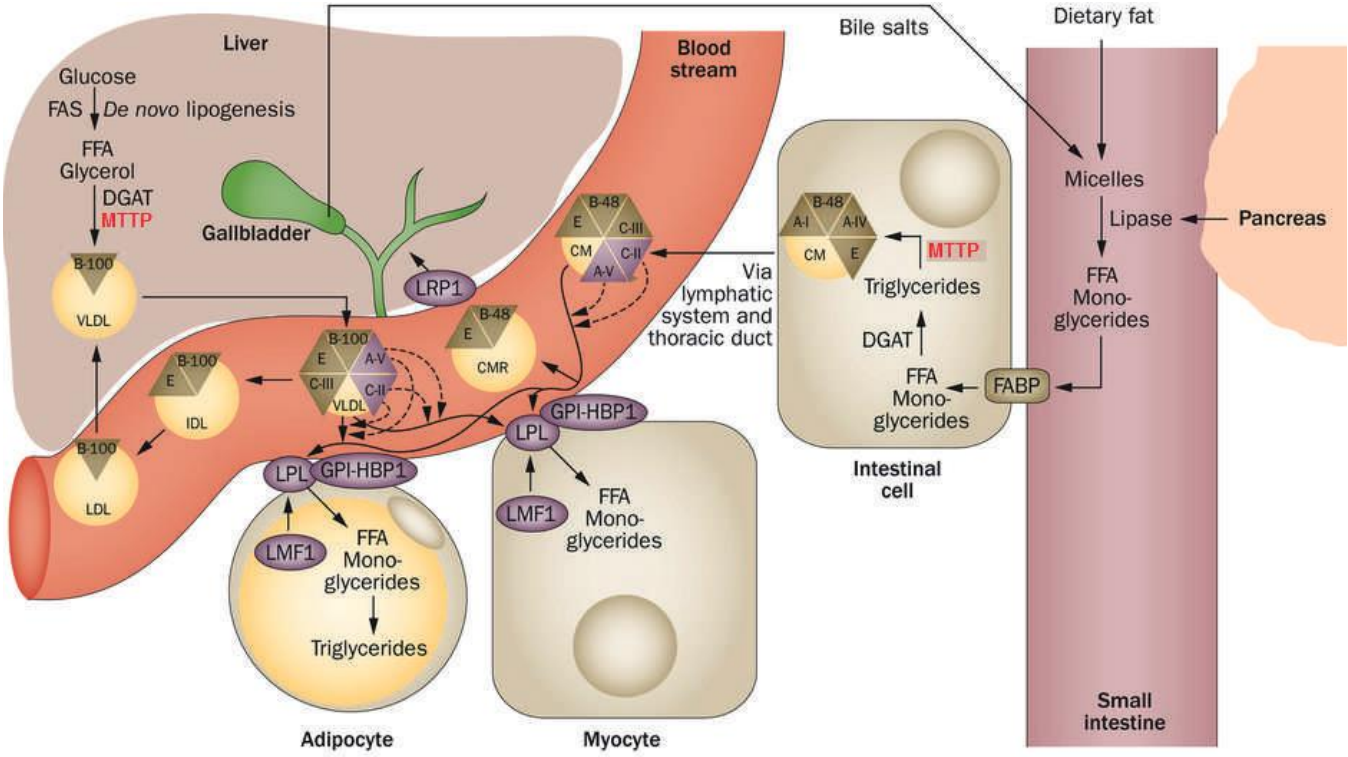


TABLE 1

Comparison of the Pharmacologic Effects, Efficacy, Safety, Adverse Effect, and Cost of Lomitapide Mesylate and Mipomersen

Study	Drug Name	Approval Time by FDA	Drug Class & Pharmacologic Effect	Efficacy	Usage	Adverse Effects	Annual Cost
FDA briefing document, NDA 203858[11]	Lomitapide mesylate	December 21, 2012	Microsomal triglyceric transfer protein inhibitor	Reduces LDL cholesterol, apo B, TC, non-HDL cholesterol in patients with HoFH; at week 26, level of LDL cholesterol fell by 40% from 336 mg/dL vs baseline190 mg/dL	5 mg oral once daily; titrate dose 10 mg, 20 mg, 40 mg, and up to 60 mg	Risk of hepatotoxicity: increase in serum transaminases (ALT and/or AST) and bilirubin, and induction of hepatic steatosis leading to progressive liver diseases, including steatohepatitis and cirrhosis	$235,000-$295,000
FDA briefing document, NDA 203568[12]	Mipomersen sodium	January 29, 2013	An oligonucleotide inhibitor of apo B-100 synthesis as a lipid-lowering medicine	Reduces LDL-C, apo B, TC, non-HDL cholesterol in patients with HoFH; on average, levels of LDL cholesterol fell by 25% during the first 26 weeks	200 mg once weekly as a subcutaneous injection	Risk of hepatotoxicity: increase in serum transaminases (ALT and/or AST) and bilirubin, and induction of hepatic steatosis leading to progressive liver diseases, including steatohepatitis and cirrhosis	$176,000

ALT, alanine aminotransferase; Apo, apolipoprotein; AST, aspartate aminotransferase; FDA, US Food and Drug Administration; HDL, high-density lipoprotein; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; TC, total cholesterol.

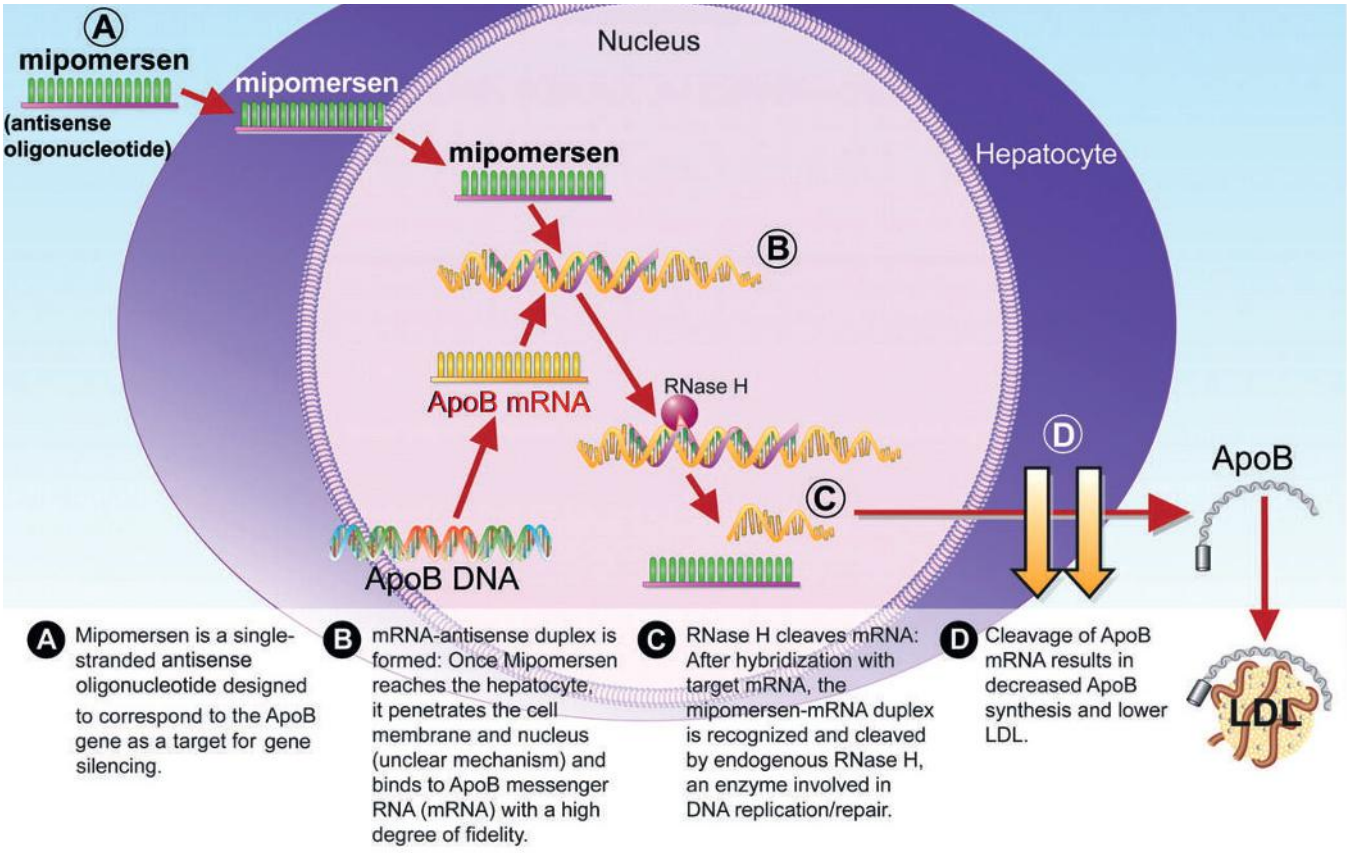


Figure 4. Mechanism of action of mipomersen in the hepatocyte. ApoB, apolipoprotein B; LDL, low-density lipoprotein; mRNA, messenger RNA; RNase H, ribonuclease H. Reprinted with permission from Kohli and Cannon.[7]

after bariatric surgery, combined with the drug effect of impairing synthesis of apo B. Because both drugs reduce the production of very low-density lipoprotein and downstream products of lipases and hydrolysis, including intermediate density lipoprotein and LDL, there is less of a burden of LDL to be cleared by LDL receptors, which are the defective cellular unit in most cases of HoFH.

Although both lomitapide mesylate and mipomersen have performed well at lowering LDL cholesterol, apo B, and total cholesterol levels in proposed two cases, the median LDL cholesterol reductions on these drugs are reported as −44% and −25%, respectively. In a prospective study of 29 HoFH patients, Cuchel and colleagues[2] reported a 44% reduction in LDL cholesterol with escalating doses of lomitapide mesylate at 56 weeks from a baseline of 336 mg/dL. In this study, 10 (34%) of 29 patients had at least one elevation in ALT or AST ≥ 3 times the upper limit of normal (ULN) and 4 (14%) of the patients had at least one elevation in ALT or AST ≥ 5 times the ULN. In a 2:1 randomized trial of mipomersen versus placebo in 51 patients with HoFH, Raal and colleagues[3] reported a 25% reduction in LDL cholesterol from a baseline of 430 mg/dL with mipomersen in a fixed dose at 200 mg per week. In this trial, 12% of patients treated with mipomersen had at least one ALT ≥ 3× ULN over the course of treatment. Additionally, the median absolute increase in hepatic fat determined by magnetic resonance imaging was 10% after 26 weeks of treatment. From previous studies, the physiologic relationship between LDL reduction with lomitapide mesylate and mipomersen and hepatic steatosis has been a predictable clinical tradeoff between LDL cholesterol-lowering and drug-induced liver injury.[8,9] Strict adherence to treatment guidelines should be practiced, as hepatic steatosis may be worsened by alcohol intake and insulin resistance.[8] The consequences of increased hepatic fat from drug therapy is unknown, but it has been reported that fatty

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steatosis can lead to chronic liver disease in the setting of biopsy-proven nonalcoholic fatty steatosis.[8] Because these two therapies are orphan drugs and have risk of hepatotoxicity, clinicians must undergo a certification process after receiving education on a Risk Evaluation and Mitigation Strategy program.[8-10] Additionally, both agents are dispensed from specialty pharmacies in the United States that require liver function testing before each monthly renewal during the first year. Subsequent years, liver function testing can be reduced to every 3 months.

Conclusions

HoFH is a rare condition that now has specific therapies that can be used in addition to conventional lipid-lowering therapies. Both lomitapide mesylate and mipomersen offer advantages and risks that can be individualized for each patient depending on his or her comorbid conditions. Advanced drug therapy for this condition holds the promise of prolongation of life and reduced rates of atherosclerotic events, and may potentially obviate the need for lipid apheresis. Future research is needed into the determinants of both maximal efficacy and drug safety with agents used for patients with HoFH. ■

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MAIN POINTS

- Homozygous familial hypercholesterolemia (HoFH) is an autosomal codominant disorder manifested by high concentrations of total cholesterol and low-density lipoprotein (LDL) cholesterol, and premature cardiovascular disease. Despite conventional lipid-lowering therapy, LDL cholesterol levels remain elevated in patients with HoFH; these patients are considered to be at high risk for cardiovascular events.
- Many patients with HoFH show only a modest response to statin drugs. Patients who are statin intolerant are particularly worrisome because alternative agents, including bile acid sequestrants, ezetimibe, and nicotinic acid, have very modest treatment effects with symptomatic side effects.
- Both lomitapide mesylate and mipomersen are indicated for treatment of patients with HoFH and can lower LDL cholesterol levels considerably when used as primary or second-line agents.
- Because these two therapies are orphan drugs and have risk of hepatotoxicity, clinicians must undergo a certification process after receiving education on a Risk Evaluation and Mitigation Strategy program.