Case Study:
Effects of Mipomersen in Combination with Lomitapide in Homozygous Familial Hypercholesterolemia

P. BARTON DUELL, MD, FNLA
President, Pacific Lipid Association
Knight Cardiovascular Institute
Associate Professor, Division of Endocrinology, Diabetes, and Clinical Nutrition
Oregon Health & Science University
Portland, OR

Mipomersen and lomitapide are specialty medications FDA-approved for the treatment of patients with homozygous familial hypercholesterolemia. Mipomersen is an antisense oligonucleotide that decreases the translation of apolipoprotein B in the liver and reduces concentrations of very-low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B, and lipoprotein(a) in plasma.[1,2] Lomitapide is a small molecule inhibitor of microsomal triglyceride transfer protein (MTP) that decreases the formation of VLDL in the hepatocyte and reduces concentrations of VLDL-C, LDL-C, non-HDL-C, and apoprotein B in plasma.[2,3] Lomitapide also inhibits the formation of chylomicrons in the enterocyte, necessitating a very-low-fat diet to avoid steatorrhea, which may produce modest additional LDL-C lowering among patients who have inducible LDL receptor activity. Both medications can cause transaminase elevations and hepatic steatosis. No studies have been conducted to assess the safety and efficacy of treatment with mipomersen in combination with lomitapide.

Patient Case

A 21-year-old man with homozygous familial hypercholesterolemia and baseline LDL-C 743 mg/dl at the age of almost 8 years had been treated long-term with a high-dose, four-drug LDL-lowering regimen consisting of rosuvastatin 40 mg daily, ezetimibe 10 mg daily, niacin extended-release (ERN) 2 grams every evening, and colesevelam 2.5 grams twice daily (BID) in combination with lifestyle modification. His plasma LDL-C concentration during treatment with this regimen had been gradually increasing from 178 mg/dl to 221 mg/dl over about four years. He had remained free of vascular complications. He has declined LDL apheresis.

Treatment with mipomersen 200 mg subcutaneously weekly was initiated as an adjunct to his existing medication regimen in October 2013. He had pain associated with the injections but otherwise tolerated the medication well, including consistently normal plasma alanine transminase (ALT) and aspartate aminotransferase (AST) concentrations. After nine months of treatment with mipomersen in combination with his four other lipid-lowering medications, his plasma LDL-C concentration was 201 mg/dl. Although this appeared to constitute only a 10 percent reduction in his LDL-C concentration, his LDL-C concentration had been increasing prior to initiating treatment with mipomersen, so it was suspected that his LDL-C concentration would have been much higher than the pretreatment level of 221 mg/dl if he had not been taking mipomersen. This possibility was supported by the finding of a 25 percent reduction in his plasma lipoprotein(a) concentration, from 198 mg/dl to 147 mg/dl, during treatment with mipomersen. Since mipomersen decreases the LDL-C substantially more than lipoprotein(a),[1] it is possible that his LDL-C may actually have been 30 to 35 percent lower in response to treatment with mipomersen.

Treatment with mipomersen was discontinued and lomitapide 5 mg daily was initiated, with titration up to 10 mg daily. Although mipomersen has a long median elimination half-life of 35 days,[4,5] the decision was made to initiate treatment with lomitapide 5 mg daily beginning about four to five weeks after his last dose of mipomersen. There were two reasons. First, we were reassured by his completely normal transaminase concentrations during the preceding nine to 10 months of treatment with mipomersen. Second, we did not want his LDL-C concentration to rise during a five- to six-month wash-out of mipomersen prior to initiating treatment with lomitapide. He initially took lomitapide 5 mg daily for two to three weeks, which he tolerated well, and we subsequently increased the dose to 10 mg daily for three to four weeks. His subsequent lab results demonstrated a dramatic reduction in his LDL-C, to 69 mg/dl, but his ALT concentration increased to 197 U/L (just below five times the upper limit of normal) (see Table 1), so treatment with lomitapide was discontinued. Hepatic ultrasonography performed about three weeks after stopping lomitapide demonstrated slightly increased hepatic echogenicity consistent with mild hepatic steatosis. His transaminase concentrations normalized and his LDL-C concentration increased to 187 mg/dl about five weeks after stopping lomitapide during continued treatment with his initial four-drug regimen, so treatment with lomitapide was resumed.

During the subsequent eight months the patient was treated with lomitapide, but he was unable to titrate above a dose of 5 mg alternating with 10 mg every other day because of increases in his transaminase concentrations greater than 2.5-fold above the upper limit of normal. The transaminase elevation was a concern, particularly in light of the finding of mild hepatic steatosis shortly after initiating treatment with lomitapide. As of August 2015 he was tolerating lomitapide 5 mg daily with normal transaminase concentrations, but his LDL-C concentration was up to 199 mg/dl, which was nearly identical to his LDL-C concentration during treatment with mipomersen 200 mg weekly and unacceptably high. Since alirocumab was approved by the FDA on July 24, he will initiate a trial of treatment with alirocumab 75 mg subcutaneously every two weeks.

This case demonstrates dramatic LDL-C lowering in response to treatment with lomitapide 10 mg daily on the shoulder of mipomersen therapy (about

Treatment added to 4-drug regimen	Total Cholesterol (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	Triglycerides (mg/dl)	ALT (U/L)	AST (U/L)	Alkaline phosphatase (U/L)	Total bilirubin (mg/dl)	Albumin (g/dl)	Total protein (g/dl)
Mipomersen 200 mg/wk for 9 months	267	201	36	149	27	16	78	0.5	3.9	7.3
Lomitapide 10 mg/d for 3-4 wk (~ 10-11 wk after last dose of mipomersen)	109	69	29	60	197	82	62	0.5	4.5	7.0
4 weeks after stopping lomitapide	237	187	30	102	35	24	66	0.4	4.6	7.1
Lomitapide 5 mg/d (5 months after last dose of mipomersen)	234	182	33	96	68	36	63	0.3	4.5	6.7
Lomitapide 5 mg/d with 10 mg every 3rd day (7 months after last dose of mipomersen)	215	161	30	118	102	47	56	0.4	4.7	7.0
Lomitapide 5 mg qod alternating with 10 mg qod (10 months after last dose of mipomersen)	177	138	26	65	97	51	51	0.5	4.6	6.5
Lomitapide 5 mg/d (1 yr after last dose of mipomersen)	239	199	25	73	31	24	60	0.6	4.6	6.8

Table 1. Changes in laboratory results over time. The patient was taking rosuvastatin 40 mg daily, ezetimibe 10 mg daily, niacin extended-release 2 grams every evening and colesevelam 2.5 grams BID in combination with lifestyle modification at all time points.

one half-life after stopping treatment with mipomersen), but with significant hepatotoxicity reflected by an ALT elevation to nearly five times the upper limit of normal within the first six to seven weeks and evidence of mild hepatic steatosis on ultrasonography. There was no evidence of hepatocellular injury manifested as an elevation in bilirubin or decrease in albumin or total protein. Moreover, the transaminase elevation was reversible within five weeks after stopping treatment with lomitapide. It is notable that lomitapide alone produced ALT elevations to 2.5 times the upper limit of normal at a mean dose of 7.5 mg daily (10 mg every other day alternating with 5 mg every other day), so it is possible that lomitapide 10 mg daily in the absence of mipomersen also may elevate his ALT concentration to five times the upper limit of normal but without the dramatic reduction in LDL-C to 69 mg/dl. These results raise the possibility that the combination of low doses of mipomersen and lomitapide may have synergistic effects that augment LDL-C lowering to levels unachievable with either drug alone. Studies are needed to verify the safety, efficacy, and appropriate doses of mipomersen in combination with lomitapide for treatment of homozygous familial hypercholesterolemia. ■

Disclosure statement: Dr. Duell has received research grants from Genzyme, Regeneron, Retrophin, and Amgen. He has received honoraria from Genzyme, Sanofi, Regeneron, Retrophin, Lilly, and Kaneka.

References are listed on page 36.