Lipid Luminations:
Emerging Therapies for Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is a disease caused by autosomal dominant defects in the genes coding for the low-density lipoprotein (LDL) receptor, apolipoprotein (Apo) B, or proprotein convertase subtilisin/kexin type 9 (PCSK9).[1] It is the most common single gene lipid disorder. FH is characterized by severely elevated blood cholesterol concentrations. Xanthelasmas, tendon xanthomas, tuberous xanthomas, and corneal arcus may be evident upon physical examination of FH patients.[1] Homozygous FH is rare, occurring in about one of every million persons. Heterozygous FH is more common, occurring in one of every 300-500 people, and in some founder communities the incidence may be as high as one in 50 to 100 persons.[1] More than 10 million people worldwide have some form of FH. Homozygotes have much higher cholesterol levels [total cholesterol (-C) typically in the range of 650-1000 mg/dL] and earlier onset of coronary artery disease than heterozygotes, who typically have total-C in the range of 350-550 mg/dL.[1] Although many patients with heterozygous FH respond well to high-dose statins, ezetimibe, and bile acid sequestrants, management of homozygous FH patients is especially difficult due to the magnitude of LDL-C reduction that is needed, and because many homozygotes are refractory to statins, the mechanism of action of which depends mainly on up-regulation of hepatic LDL receptors. Several therapies are available, or in development, for the treatment of FH. In this article, we will briefly describe LDL-apheresis, PCSK9 inhibitors, mipomersen, and lomitapide, largely reflecting a summary of presentations given in a session on emerging therapies for LDL-C at the 2012 National Lipid Association Annual Scientific Sessions.[2]

LDL-apheresis. LDL-apheresis is a Food and Drug Administration (FDA)-approved therapy for patients with homozygous FH and severe heterozygous FH. LDL-apheresis is a process which selectively removes apoB-containing lipoproteins from the circulation, including LDL, lipoprotein (a), and very-low-density lipoprotein (VLDL) particles, through Heparin-induced Extracorporal LDL Precipitation (HELP®)[3] or extracorporal precipitation with dextran sulfate (Liposorber®).[4] LDL-apheresis produces an acute fall in LDL-C levels of 70-80%, but there is a rapid rebound effect, and concentrations return to initial levels by ~2 weeks. When repeated once-a-week in patients with homozygous FH and every-other-week in patients with heterozygous FH, LDL-apheresis typically produces a time-average LDL-C reduction of ~40-60% (Table 1). Studies of LDL-apheresis have been small and non-randomized, but the results have been

	Reductions from Baseline (%)		
Therapy	**LDL-C**	**apoB**	**Lp(a)**
LDL-apheresis	40-60	40-60	50-80
PCSK9 inhibitor	50-70	50-60	30-40
Mipomersen	25-37	26-38	21-33
Lomitapide	40-50	40-50	~10

Abbreviations: Apo = apolipoprotein, FH = familial hypercholesterolemia, LDL-C = low-density lipoprotein cholesterol, Lp(a) = lipoprotein (a), PCSK9 = proprotein convertase subtilisin/kexin type 9

Table 1. Summary of ranges of approximate LDL-C, apoB, and Lp(a) reductions observed in studies of emerging therapies for FH.

consistent with those from statin trials. Although data from randomized, controlled clinical trials are not available, homozygous and severe heterozygous FH patients treated with LDL-apheresis have shown significant reductions in cardiac morbidity compared to those who have not received the treatment.[5-7] LDL-apheresis has been approved for use in the United States for ~15 years.

PCSK9 inhibition. An emerging therapy for FH is a monoclonal antibody to PCSK9. PCSK9 is a protein secreted by the hepatocyte which "chaperones" the LDL receptor from the cell surface, into the clathrin-coated pit, and into the cell for lysosomal degradation.[8] Gain-of-function and loss-of-function mutations in the gene for PCSK9 have been described. Gain-of-function mutations are rare and result in fewer LDL receptors and increased LDL-C levels. Loss-of-function mutations lead to reduced LDL receptor degradation, resulting in more LDL receptors on the surface of the liver, life-long decreased LDL-C concentrations, and reduced cardiovascular risk. In loss-of-function mutation carriers, LDL-C levels have been shown to be 15 to 28% lower and incident coronary heart disease was reduced by 47 to 88% compared with individuals lacking PCSK9 gene mutations.[9]

Monoclonal antibodies to PCSK9 mimic the effects of genetic mutations. In the monoclonal antibody approach, an antibody to PCSK9 binds to the PCSK9 protein, thereby inhibiting its effect on the LDL receptor.[10] Results from phase 1 trials have demonstrated that an injectable monoclonal antibody to PCSK9 was capable of lowering LDL-C by up to 70% above the level achieved by statin therapy, and was well-tolerated with few instances of elevated liver enzymes and injection site skin reactions.[10,11] Patients with statin intolerance, those who cannot achieve an adequate LDL-C level with existing therapy, who have refractory hypercholesterolemia, or who may otherwise require LDL-apheresis, would all be expected to respond favorably to PCSK9 inhibition. However, because PCSK9 acts on the LDL receptor, the effects of PCSK9 inhibition in patients with homozygous FH who lack functioning LDL receptors may be limited. Clinical outcome trials of PCSK9 monoclonal antibodies are highly anticipated. Other methods that target PCSK9 are also in development, including antisense oligonucleotide technology.[12]

Antisense therapy. Mipomersen is an antisense oligonucleotide injectable drug which is under evaluation for the treatment of homozygous FH and severe heterozygous FH.[13] Mipomersen is complementary in sequence to a segment of the human apoB-100 messenger ribonucleic acid (mRNA).[14] It specifically binds to the mRNA and blocks translation of the gene product.[15] Decreasing the production of apoB-100 reduces the production of VLDL in the liver, which consequently reduces circulating levels of atherogenic VLDL remnants, intermediate density lipoproteins, LDL and lipoprotein (a) particles. Results from phase 3 trials conducted in patients with homozygous FH, severe hypercholesterolemia, heterozygous FH with coronary artery disease, and hypercholesterolemia at high risk for coronary artery disease have indicated that, when added to maximally tolerated lipid-lowering drug therapy, mipomersen reduced concentrations of all apoB-containing atherogenic lipoproteins.[16-19] The average LDL-C reduction was >100 mg/dL in homozygous FH and severe hypercholesterolemia populations, and the effects were consistent across all patient populations. The most frequently observed adverse events occurring on-treatment were mild-to-moderate injection site reactions and flu-like symptoms. To date, the safety and tolerability of mipomersen has been examined up to 104 weeks, and the results appear to support the suitability of mipomersen for the treatment of FH, although longer term studies will be needed to more fully evaluate the benefits and risks, particularly if use is to be extended beyond homozygous FH.[20] Additionally, a potential safety concern was raised during a recent FDA review, an increased frequency of cancer in subjects treated with mipomersen in clinical trials, although it is uncertain whether this association is causal.[21]

Microsomal triglyceride transfer protein inhibition. Another drug currently under evaluation as an adjunct to a low-fat diet and other lipid-lowering therapies for reducing LDL-C in patients with homozygous

FH and severe hypertriglyceridemias is the orphan drug lomitapide. Lomitapide is a small molecule microsomal triglyceride transfer protein (MTP) inhibitor.[22] MTP is located in the endoplasmic reticulum of enterocytes and hepatocytes, and is necessary for the formation of chylomicron and VLDL particles. Results from recent phase 2 and 3 studies of lomitapide (formerly BMS-201038 and AEGR-733) demonstrate its efficacy as add-on therapy to substantially reduce atherogenic lipoprotein concentrations in FH patients.[22-24] Total-C, LDL-C, and apoB declined from baseline by >40% at 26 weeks and reductions were maintained for another 52 weeks.[23] Gastrointestinal disorders were the most frequent side effects and the most common reason for failure to tolerate lomitapide dose escalation. However, a concern regarding the use of lomitapide is its tendency to increase hepatic fat dose-dependently, although the effect varies considerably between patients and hepatic fat declined during a washout period. It is anticipated that long-term safety and cardiovascular benefit studies will be required by the FDA. In addition to treating adult patients with homozygous FH, other populations in which MTP inhibitors may be considered are severe heterozygous FH, hypercholesterolemic patients who are statin intolerant, and individuals with severe hypertriglyceridemia caused by lipoprotein lipase deficiency. Initial approval of lomitapide (and mipomersen) is being sought for adult patients, however, children with homozygous FH represent a particularly important group to which the indication could eventually be extended since they often develop coronary heart disease in their 20s or earlier.[25]

In summary, the emergence of new lipid-altering therapies that act in series and in parallel with available agents may provide more effective LDL-C lowering in patients with FH who do not tolerate high-dose statins, or for whom the magnitude of LDL-C lowering needed is beyond the degree which can be achieved with current regimens. ■

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References listed on page 32.