Novel Therapeutics May Lower LDL in Familial Hypercholesterolemia

Written by Rita Buckley

Familial combined hyperlipidemia is a highly atherogenic disorder that affects 1% to 2% of the Western world [Shoulders CC et al. *Hum Mol Genet 2004*]. It occurs in approximately 20% of patients who develop coronary heart disease before age 60 [Aouizerat BE et al. *Am J Hum Genet* 1999].

Patrick M. Moriarty, MD, University of Kansas Medical Center, Lawrence, Kansas, USA, explained that treatment of familial hypercholesterolemia (FH) represents an unmet medical need. Statins have been shown to improve survival and reduce the risk of myocardial infarction (MI) in heterozygous familial hypercholesterolemia (HeFH) [Versmissen J et al. *BMJ* 2008] and prolong survival in homozygous familial hypercholesterolemia (HoFH) [Raal FJ et al. *Circulation* 2011]. Emerging therapies include apolipoprotein B (ApoB) inhibitors, microsomal triglyceride transfer protein (MTP) inhibitors, and proprotein convertase subtilism kexin 9 (PCSK9) inhibitors [Alonso R et al. *Expert Rev Cardiovasc Ther* 2013].

MIPOMERSEN, AN INJECTABLE APOLIPOPROTEIN B-100 INHIBITOR

John J.P. Kastelein, MD, PhD, University of Amsterdam, Amsterdam, The Netherlands, spoke about the benefits of mipomersen, a 20-mer phosphorothioate antisense oligonucleotide that is complementary in sequence to a segment of the human ApoB mRNA [Kastelein JJ et al. *Circulation* 2006]. Mipomersen is administered as a subcutaneous injection and has been shown to reduce low-density lipoprotein cholesterol (LDL-C), apoB, total cholesterol, and non-high-density lipoprotein cholesterol (non-HDL-C) levels in patients with HoFH, heterozygous FH as well as high-risk hypercholesterolemic patients. It has been developed as an adjunct to standard therapies including a statin; however, its indication was limited by regulatory authorities due to its many side effects, including liver enzyme abnormalities and accumulation of fat in the liver [Raal FJ et al. *Lancet* 2010; Stein EA et al. *Circulation* 2012].

In a randomized, double-blind, multicenter, placebo-controlled, Phase 3 study in which 34 HoFH patients who were already receiving the maximum tolerated dose of a lipid-lowering drug were randomly assigned to mipomersen 200 mg subcutaneously every week or placebo for 26 weeks, the mean percent change in LDL-C concentration was significantly greater with the addition of mipomersen (–24.7%; 95% CI, –31.6 to –17.7) compared with placebo (–3.3%; 95% CI, –12.1 to 5.5; p=0.0003) [Raal FJ et al. *Lancet* 2010].

LOMITAPIDE, AN ORAL MICROSOMALTRANSFER PROTEIN INHIBITOR

Michael Davidson, MD, University of Chicago, Chicago, Illinois, USA, discussed the oral MTP inhibitor, lomitapide. MTP, an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum, is responsible for binding and shuttling individual lipid molecules between membranes [Hussain MM et al. *J Lipid Res* 2003]. Normal concentrations and function of MTP are necessary for the proper assembly and secretion of apoB-containing lipoproteins in the liver and intestines [Liao W et al. *J Lipid Res* 2003].

A dose-escalation study to examine the safety, tolerability, and effects on lipid levels of lomitapide (BMS-201038), an inhibitor of the miscrosomal triglyceride transfer protein, showed that all patients tolerated titration to the highest dose of 1.0 mg/kg/day. Treatment at this dose decreased LDL-C levels by 51% and apoB levels by 56% from baseline (p<0.001 for both comparisons) [Cuchel M et al. *N Engl J Med* 2007]. Serious adverse effects associated with lomitapide included hepatic fat accumulation and elevated liver aminotransferase levels. Thus as with mipomersen, lomitapide has received FDA approval for use only in patients with HoFH due to adverse events which include elevations in serum transaminase and hepatic steatosis and gastrointestinal side effects [Robinson JG. *J Manag Care Pharm* 2013].

CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS

Christopher Cannon, MD, Harvard Medical School, Boston, Massachusetts, USA, discussed the oral CETP inhibitors. The ILLUMINATE trial studied torcetrapib, and, in spite of favorable effects on lipids including a 72% increase in HDL and a 25% reduction in LDL-C, was stopped early due to increased major cardiovascular (CV) events and higher blood pressure [ILLUMINATE; Barter PJ et al. *N Engl J Med* 2007]. Later studies suggested that the adverse effects of torcetrapib came from molecule-specific off-target effects on the adrenal gland, and were not related to the direct effect of CETP inhibition [Krishna R et al. *Lancet* 2007].

Dalcetrapib, the second CETP inhibitor developed, was evaluated in the dal-OUTCOMES trial in patients (n=15,871) with a recent acute coronary syndrome. A substantial increase in HDL levels was seen with dalcetrapib compared with placebo (31% to 40% vs 4% to 11%), and no off-target effects on the adrenal gland or hypertension were observed. However, dalcetrapib did

not reduce the primary composite outcome of death from coronary heart disease, a major nonfatal coronary event or ischemic stroke (8.3% with dalcetrapib vs 8.0% with placebo; HR, 1.04; 95% CI, 0.93 to 1.16; p=0.52) [Schwartz GG et al. *N Engl J Med* 2012].

Anacetrapib is the third CETP inhibitor. It increases HDL-C by over 100% and lowers LDL-C by 30% to 40% as monotherapy and when coadministered with statins [Cannon CP et al. *N Engl J Med* 2010]. In a recent 1.5-year safety study in ~1600 patients with CV disease [Cannon CP et al. *N Engl J Med* 2010], anacetrapib treatment had no effect on blood pressure, electrolytes, or aldosterone, and the distribution of CV events suggested that anacetrapib treatment would not be associated with an increase of CV risk as was seen with torcetrapib.

A randomized controlled trial in 398 patients with elevated LDL-C or low HDL-C of a fourth CETP inhibitor, evacetrapib, showed that evacetrapib monotherapy produced dose-dependent increases in HDL-C of 54% to 129% and decreases in LDL-C of –14% to –36% (both p< 0.001 compared with placebo) [Nicholls SJ et al. *JAMA* 2011].

Both anacetrapib and evacetrapib are currently involved in ongoing Phase 3 trials (Table 1).

PROPROTEIN CONVERTASE SUBTILISM KEXIN 9 INHIBITORS

James M. McKenney, PharmD, Virginia Commonwealth University, Richmond, Virginia, USA, discussed PCSK9 inhibitors, a novel therapy for lowering LDL-C. PCSK9 regulates cholesterol and/or lipid homeostasis via cleavage at nonbasic residues or through induced degeneration of receptors. Reduction in LDL-C levels with PCSK9 is associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non–lipid-related CV risk factors [Cohen JC et al. *N Engl J Med* 2006].

In the LAPLACE-TIMI 57 Phase 2, multicenter, dose-ranging study, 631 stable patients with hypercholesterolemia on a statin, were randomly assigned to AMG 145, a fully human monoclonal IgG2 antibody against PCSK9, administered subcutaneously every 2 (70, 105, or 150 mg) or 4 weeks (280, 350, or 420 mg) or matching placebo injections [Giugliano RP et al. *Lancet* 2012]. At the end of the 12-week period, largely dose-dependent reductions in the mean LDL-C concentrations for the every 2-week regimens ranged from 42% to 66% and from 42% to 50% for the every 4-week regimens (p<0.0001 for each dose vs placebo). These results suggest that PCSK9 inhibition could be a new model in lipid management and is being evaluated in ongoing Phase 3 clinical trials.

SAR236553/REGN727, another injectable monoclonal antibody to PCSK9, also showed promising results in a multicenter, randomized, placebo-controlled Phase 2 trial in adults with HeFH and LDL-C concentrations of 100 mg/dL or higher on stable diet and statin dose, with or without ezetimibe. Patients were randomized to receive subcutaneous REGN727 150, 200, or 300 mg every 4 weeks, or 150 mg every 2 weeks, or matching placebo every 2 weeks (ratio 1:1:1:1:1). The primary endpoint of LDL-C reduction from baseline to Week 12 was 29% for 150 mg every 4 weeks (p=0.0113), 32% for 200 g every 4 weeks (p=0.0035), 43% for 300 mg every 4 weeks (p<0.0001), and 68% for 150 mg every 2 weeks (p<0.0001), compared with 11% with placebo. [Stein EA et al. *Lancet* 2012]. A Phase 3 trial is underway to evaluate the CV effects and long-term safety of this compound on a background of statin therapy.

Until recently, many patients with HeFH and HoFH had difficultly achieving adequate reduction in LDL-C. Mipomersen and lomitapide have recently received FDA approval for the treatment of HoFH and offer new options as adjuncts to high-dose statins and second-line treatments. As emerging therapies such as CETP inhibitors and PCSK9 inhibitors continue development, options will increase for patients with HoFH, HeFH, and other patients with severe dyslipidemia.

Table 1. Ongoing Phase 3 Trials of Anacetrapib and Evacetrapib

	Anacetrapib	Evacetrapib
Name (ID)	REVEAL (NCT01252953)	ACCELERATE (NCT01687998)
Dose	100 mg daily	130 mg daily
Sample size	30,000	11,000
Inclusion	Age ≥50yrs History of MI Stroke or cerebral revascularization PAD repair/revascularization DM with symptomatic CAD	Age ≥18yrs History of ACS (30 to 365 days) Cerebrovascular atherosclerotic disease PAD DM with documented CAD
PEP	Coronary death, MI, or coronary revascularization	CV death, MI, stroke, coronary revascularization, or hospitalization for UA
Study duration	Median ~4 yrs ≥1900 primary endpoints	Median ~2yrs ≥1136 primary endpoints

ACS=acute coronary syndrome; CAD=coronary artery disease; CV=cardiovascular; DM=diabetes mellitus; MI=myocardial infarction; PAD=peripheral arterial disease; UA=unstable angina.