Monoclonal Antibody to PCSK9 Offers New Approach to Treating Hypercholesterolemia

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Hypercholesterolemia, particularly an increased level of low-density lipoprotein cholesterol (LDL-C) is associated with elevated cardiovascular (CV) risk. Individuals with genetic lifelong lower levels of LDL-C are associated with a reduced risk of CV events. In addition, the reduction in coronary heart disease (CHD) risk is proportional to the decrease in LDL-C over the time period of LDL-C reduction. Statins are often used to therapeutically lower LDL-C levels, but individuals with lifelong lower LDL-C levels due to genetic variants have three times the protection from CHD as do those who begin statin therapy later in life. In a meta-analysis, the effect on reduced CHD risk was directly proportional to the decrease in LDL-C associated with each allele [Ference BA et al. *J Am Coll Cardiol* 2012].

Gregory S. Thomas MD, MPH, Memorial Care Heart and Vascular Institute, University of California, Irvine, Irvine, California, USA, questioned whether we should start treating patients with drugs, diet, and exercise earlier in their life span, and whether treatment decisions should be based on the 10-year or lifetime CHD risk. Dr. Thomas presented examples of individuals with heterozygous familial hyperlipidemia (HeFH), who, in contrast to those with alleles associated with lifetime lower LDL-C levels, have lifetime higher LDL-C levels. In addition to hyperlipidemia, people with HeFH experience myocardial infarctions (MI) at an early age, and may undergo repeat coronary artery bypass grafting (CABG) and stenting.

Normally, LDL receptors are expressed on the cell surface, primarily on liver cells. LDL receptors "pick up" LDL particles; via endocytosis into a clathrin-coated vesicle, the LDL is ultimately degraded in a lysosome while the LDL receptor is recycled via an endosome back to the cell surface where it can continue to regulate LDL levels. This process is regulated by the sterol regulatory element binding protein (SREBP) in the nucleus.

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that affects the recycling of LDL receptors. Like the LDL receptor, PCSK9 is also regulated by SREBP. Circulating PCSK9 binds to the extracellular domain of the LDL receptor, followed by transport to an intracellular lysosome rather than a clathrin-coated vesicle, where the LDL receptor is degraded, rather than being recycled. Thus, increased PCSK9 activity results in fewer LDL receptors available on the cell surface to remove LDL from circulation.

Individuals with nonsense mutations in the PCSK9 gene have reduced levels of LDL-C and a significantly reduced risk of CHD [Cohen JC et al. *N Engl J Med* 2006]. Among 3363 black subjects, mean LDL-C was 28% lower and CHD risk was reduced by 88% in the 2.6% who had a PCSK9 nonsense mutation as compared with those subjects without the nonsense mutation (HR, 0.11; 95% Cl, 0.24 to 0.97; p=0.03). Of 9524 white subjects, 3.2% had a PCSK9 sequence mutation. This mutation was associated with a 15% lower LDL-C and a 47% lower CHD event rate (adjusted HR, 0.50; 95% Cl, 0.32 to 0.79; p=0.003). This observation suggested that inactivating PCSK9 in individuals with hypercholesterolemia might be a strategy to lower LDL-C levels in individuals with high LDL-C levels.

SAR236553/REGN727 (alirocumab) is a fully humanized monoclonal antibody that binds to circulating PCSK9 and prevents it from binding to the LDL receptor. Binding of SAR236553/REGN727 to PCSK9 allows normal recycling of the LDL receptor, so rather than being degraded, the LDL receptor continues to remove LDL from circulation.

Clinical trials have been conducted of SAR236553/REGN727, which is administered by subcutaneous injection. SAR236553/REGN727 lowered LDL-C in normal healthy volunteers [Stein EA et al. *N Engl J Med* 2012]. A dose-finding study in patients with HeFH showed SAR236553/REGN727 lowered LDL-C without adverse effects on liver function tests [Stein

EA et al. *Lancet* 2012]. Adding SAR236553/REGN727 to atorvastatin resulted in further lowering of LDL-C levels in patients with primary hypercholesterolemia [Roth EM et al. *N Engl J Med* 2012]. In this study, adverse events included rash that responded to antihistamine administration, and injection-site reactions in three of the 61 patients. One patient with mild AST elevation at baseline had a further AST elevation. In another Phase 2 study, one patient experienced vasculitis that resolved with treatment [McKenney JM et al. *J Am Coll Cardiol* 2012]. Two weeks before and after there were no anti-SAR236553/REGN727 antibodies detectable; however, at Week 20, a follow-up assessment detected minimal (titer of 30) anti-SAR236553/REGN727 antibodies.

The Phase 3 Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab SAR236553 [REGN727]) trial [Odyssey Outcomes; NCT01663402] is testing a 150-mg dose of SAR236553/REGN727 administered subcutaneously Q2W. This randomized, double-blind, placebo-controlled, parallel-group trial will evaluate the effect of SAR236553/REGN727 compared wih placebo on the occurrence of CV events. The planned enrollment is 18,000 individuals who have had an acute coronary syndrome (ACS) event 4 to 16 weeks prior to random assignment and who are being treated for dyslipidemia. The primary composite endpoint of CV events includes CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, and unstable angina requiring hospitalization. The trial completion date is estimated to be 2018. Dr. Thomas suggested that the initial FDA approval for SAR236553/REGN727 may be for HeFH because statins do not achieve sufficiently low levels of LDL-C for these individuals.

The safety and efficacy of SAR236553/REGN727 continues to be evaluated in a number of clinical trials, alone and in combination with other cholesterol-lowering agents such as statins, fibrates, and cholesterol absorption inhibitors, and in patients with HeFH and those with other causes of hypercholesterolemia. It will be necessary to determine the long-term effects of administration of SAR236553/REGN727, given the reports of injection-site reactions. Patient acceptability may also be an issue, as the current administration scheme requires subcutaneous injection every 2 weeks, presumably for life. Similar Phase 2 studies have been conducted and Phase 3 trials are underway with AMG 145, a monoclonal antibody administered either every 2 or every 4 weeks.

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