Emerging low-density lipoprotein therapies: Targeting PCSK9 for low-density lipoprotein reduction

Michael H. Davidson, MD, FACC, FNLA*

Diplomate of the American Board of Lipidology, The University of Chicago Pritzker School of Medicine, 515 N. State Street, Suite 2700, Chicago, IL 60654, USA

KEYWORDS: Familial hypercholesterolemia; Low-density lipoprotein cholesterol; Monoclonal antibody; Proprotein convertase subtilisin/kexin type 9

Abstract: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein secreted by the hepatocyte that regulates the surface expression of low-density lipoprotein (LDL) receptors by targeting them for lysosomal degradation. Statins enhance PCSK9 synthesis, an effect that blunts the LDL-cholesterol (-C)–lowering effectiveness of statins. Loss-of-function mutations in the PCSK9 gene produce lifelong low levels of LDL-C and reduce cardiovascular risk. Monoclonal antibodies to PCSK9, which mimic the effects of genetic mutations by inhibiting PCSK9, are in clinical trial development. Two different commercial development programs have demonstrated significant success in lowering LDL-C in phase 1 and 2 trials with similar agents: REGN727/SAR236553 (REGN727) and, more recently, AMG 145. When administered subcutaneously at doses ranging from 50 to 150 mg every 2 weeks or 200 to 400 mg every 4 weeks, these agents produced similar dose-responses in LDL-C lowering. In hypercholesterolemic patients, LDL-C reductions ranged up to 60%, and, as would be expected, an even greater response was reported for statin-treated hypercholesterolemic patients—up to 70% decrease. LDL-C has typically shown a gradual increase after the nadir as monoclonal antibodies are cleared from the circulation. Results to date indicate that the PCSK9 monoclonal antibody approach appears safe, well-tolerated, and profoundly lowers LDL-C levels while also favorably altering apolipoprotein B, triglycerides, lipoprotein (a), and high-density lipoprotein-C. It is expected to meet an important clinical need for patients unable to achieve adequate LDL-C-lowering with currently available therapies.

Low-density lipoprotein (LDL) is associated with many genetic mutations or polymorphisms that lead to either increased or reduced levels of LDL cholesterol (-C).1-4 One of the polymorphisms leading to low levels of LDL-C is a mutation in the gene for proprotein convertase subtilisin/kexin type 9 (PCSK9).5 Loss-of-function mutations in this gene lead to lifelong low levels of LDL-C, which have been associated with substantial reductions in risk for ischemic cardiovascular disease.3,5,6 Clinical trials are underway to explore a monoclonal antibody approach of targeting PCSK9 with the intent of markedly reducing LDL-C.7

Mechanism of action of PCSK9

The hepatic LDL receptor plays a central role in cholesterol homeostasis.8-10 It is a large, complex protein with a binding domain for apolipoprotein (Apo) B. This binding domain is in which most mutations in the LDL receptor occur. After Apo B (as part of an Apo B-containing lipoprotein) binds to the LDL receptor, the receptor–Apo B complex is internalized in a clathrin-coated pit and enters the hepatocyte.8,10,11 Clathrin then dissociates from the LDL receptor, and the Apo B particle undergoes lysosomal degradation, releasing cholesterol. The LDL receptor is recycled back to the surface of the hepatocyte, where it can again bind with Apo B particles, enabling efficient clearance of LDL from the circulation. PCSK9 is a protein

* Corresponding author.
E-mail address: mdavidso@medicine.bsd.uchicago.edu
Submitted December 5, 2012. Accepted for publication March 20, 2013.
secreted by the hepatocyte that “chaperones” the LDL receptor from the cell surface, into the coated pit, and into the cell for degradation and recycling.9,12,13 PCSK9 regulates the surface expression of LDL receptors by targeting them for lysosomal degradation. Statins, bile acid sequestrants, and ezetimibe stimulate LDL receptor up-regulation by decreasing the amount of cholesterol in the hepatocyte. This is a tightly regulated system; however, in a counter-regulatory action by the liver, statins also produce PCSK9 up-regulation.14 Thus, the potential reduction in LDL-C provided by some LDL-C–lowering drugs is limited by this compensatory increase in PCSK9.

Gain-of-function and loss-of-function mutations in PCSK9 have been described.13 Gain-of-function mutations, which are rare, result in fewer LDL receptors and increased LDL-C.15 Loss-of-function PCSK9 mutations lead to decreased LDL receptor degradation, resulting in more LDL receptors residing on the surface of the liver and lower LDL-C concentrations. LDL-C was 15% to 28% lower and ischemic heart disease incidence was reduced by 47% to 88% in PCSK9 loss-of-function carriers compared with those lacking such mutations.3 Monoclonal antibody techniques, similar to those used in other areas of medicine such as anti-tumor necrosis factor for neutralizing the inflammatory effects of tumor necrosis factor in rheumatoid arthritis and inflammatory bowel disease, have been used to create products which manipulate PCSK9 levels. In the case of PCSK9, a monoclonal antibody binds to the PCSK9 protein, thereby inhibiting its effect on the LDL receptor (Fig. 1).16

Monoclonal antibody to PCSK9

Several monoclonal antibodies to PCSK9 are in clinical trial development. This article is a summary of a presentation on PCSK9 inhibition that was given at the 2012 National Lipid Association Annual Scientific Sessions. At that time, most of the published data came from studies of REGN727/SAR236553 (REGN727; Regeneron Pharmaceuticals, Inc. [Tarrytown, NY] and Sanofi-Aventis [Reston, VA]) and were thus emphasized in the presentation. More recently, data from phase 1 and 2 trials of AMG 145 (Amgen, Washington, DC), another fully human monoclonal antibody to PCSK9, have been published and are described briefly in this report, although they were not part of the original presentation.

In the first set of phase 1 studies of a PCSK9 monoclonal antibody in humans, a group of healthy volunteers were administered single-dose intravenous or subcutaneous REGN727 injections (intravenous results are not shown here) and another group of patients with heterozygous familial hypercholesterolemia and nonfamilial hypercholesterolemia, who were following a modified diet, were administered multiple subcutaneous REGN727 injections on days 1, 29, and 43.17 In these studies the administration of REGN727 led to profound effects on LDL-C concentration. Notably, a single dose in healthy volunteers led to 50%-70% reductions in LDL-C (Fig. 2).17

In a 12-week placebo-controlled study in which REGN727 was injected every 2 weeks (Q2W) or Q4W in patients with primary hypercholesterolemia, McKenney et al18 showed a 30.5% LDL-C reduction 2 weeks after the initial 50-mg Q2W dose that decreased further to a 39.6% change from baseline at 12 weeks (Fig. 3). LDL-C levels after 12 weeks of 100- and 150-mg Q2W doses and 200- and 300-mg Q4W doses decreased by 64.2%, 72.4%, 43.2%, and 47.7%, respectively. These were the mean responses over time; however, the observed pattern was that upon injection of the PCSK9 monoclonal antibody there was a large decrease in LDL-C levels followed by a
gradual rebound as the monoclonal antibodies were cleared from the circulation. In addition to reductions in LDL-C, triglycerides decreased slightly (−8.4% with 300 mg), high-density lipoprotein-C increased (8.5% with 300 mg), and Apo A1 levels increased at the greatest dose (4.2% with 300 mg). The incidence of treatment-emergent adverse events was 45% in the group receiving placebo, 60% in the 50-mg Q2W, 65% in the 100-mg Q2W, 61% in the 150-mg Q2W, 67% in the 200-mg Q4W, and 47% in the 300-mg Q4W dosing groups. There were no instances of elevated liver enzymes (alanine or aspartate aminotransferase) greater than 3 times the upper limit of normal (>3 × ULN) or creatine kinase (>10 × ULN) associated with administration of the PCSK9 antibody; <1% of subjects reported muscle pain or weakness. Injection-site reactions occurred in the PCSK9 antibody groups but were generally mild and nonprogressive.

A placebo-controlled statin combination study investigated the effects of 150 mg of REGN727 Q2W for 8 weeks plus 80 mg/d atorvastatin or a maintenance dose of 10 mg/d atorvastatin (Fig. 4). In the group receiving atorvastatin 80 mg/d plus placebo, there was a decrease in LDL-C of 17.3% compared with a 73.2% reduction in LDL-C in the group receiving atorvastatin 80 mg/d plus REGN727. With the REGN727 plus atorvastatin 10 mg/d combination, LDL-C was decreased by 66.2%. In addition to its effectiveness for lowering LDL-C, treatment with REGN727 also significantly lowered Apo B, non–high-density lipoprotein-C, lipoprotein (a), and triglycerides. The mechanism accounting for the 30%–40% reduction in lipoprotein (a) is not clearly understood. Safety and tolerability results for the combination of atorvastatin plus REGN727 were also favorable. Few patients had elevated liver enzymes (one each with aspartate aminotransferase elevation >3 × ULN, alkaline
phosphatase >1.5× ULN, and total bilirubin >1.5× ULN), none had significantly increased creatine kinase, and there was just one report of a serious treatment-emergent adverse event. Injection site skin reactions were also rare and mild.

Results from phase 1 and 2 trials of AMG 145 also demonstrate the safety and efficacy of this PCSK9 inhibitor.20-24 In a phase 2 trial reported by Koren et al23 of 406 patients with hypercholesterolemia not receiving concurrent lipid-lowering treatment, AMG 145 administered subcutaneously for 12 weeks at 70, 105, or 140 mg Q2W or 280, 350, or 420 mg Q4W significantly reduced LDL-C by ~40%-50% in all dose groups (P < .001 for all doses vs. placebo or vs. 10 mg/d ezetimibe). Treatment-emergent adverse events occurred in 50% of patients in the AMG 145 groups compared with 46% of those in the placebo group and 58% receiving ezetimibe. In a large dose-ranging phase 2 trial of 631 men and women with hypercholesterolemia who were receiving statins (with and without ezetimibe), AMG 145 administered at 70, 105, or 140 mg Q2W for 12 weeks reduced LDL-C by 42 to 66% (P < .0001 for each dose vs. placebo) and AMG 145 at 280, 350, and 420 mg Q4W for 12 weeks resulted in LDL-C reductions ranging from 42 to 50% (P < .0001 for each dose vs. placebo; Fig. 5).24 The frequencies of treatment-related adverse events with AMG 145 and placebo were similar (8% and 7%, respectively), and none were severe or life-threatening.

**Conclusion and future perspectives**

In summary, these results demonstrated that a monoclonal antibody to PCSK9 was capable of lowering LDL-C by up to 70% above the level achieved by statin therapy. There are at least 3 monoclonal antibodies that inhibit PCSK9 activity as well as an antisense approach in human trials.25,26 The monoclonal antibody approach is expected to meet an important clinical need for LDL-C lowering in patients with statin intolerance, those who cannot achieve an adequate LDL-C level with existing therapy, refractory hypercholesterolemia, and those who may otherwise require LDL apheresis. Clinical outcome trials of PCSK9 monoclonal antibodies are highly anticipated. A drug such as this, which has the potential of producing LDL-C levels as low as 25 mg/dL, would be expected to be associated with a dramatic reduction in cardiovascular risk. There are a multitude of other genes affecting lipid metabolism,27 and investigating the effects of additional genetic variants could potentially lead to the development of more novel therapeutic targets for managing dyslipidemia.

![Figure 5](image-url)
Financial disclosures

Dr. Davidson has received consulting fees from Amgen, Merck & Co., Roche Pharmaceuticals, and Sanofi-Aventis and has ownership interest in Omthera Pharmaceuticals.

References