A New Approach to PCSK9 Therapeutics

Nan Wang, Alan R. Tall

PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition is an effective therapy to reduce low-density lipoprotein cholesterol and cardiovascular events. A recent study shows that 1 or 2 doses of inclisiran, a long-acting synthetic small-interfering RNA that selectively targets hepatic PCSK9, causes a sustained reduction of plasma low-density lipoprotein cholesterol for ≤6 months. Pending further studies of safety and efficacy, this may represent an important addition to the armamentarium for inhibiting PCSK9.

Genetic studies showed that gain-of-function mutations in PCSK9 (propotein convertase subtilisin/kexin type 9) lead to a high low-density lipoprotein cholesterol (LDL-C) level and premature coronary heart disease, whereas loss-of-function variants are associated with low LDL-C level and reduced coronary heart disease, identifying PCSK9 as a therapeutic target. The discovery in transgenic mice that PCSK9 is secreted by hepatocytes and enters the circulation laid the foundation for a therapeutic approach using PCSK9 monoclonal antibodies (mAbs). PCSK9 mAbs act by binding to extracellular PCSK9 and preventing its interaction with hepatic LDL receptors. This led to the successful development and US Food and Drug Administration approval of PCSK9 mAbs for use as monthly injections in adult patients with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic cardiovascular disease that requires treatment for LDL-C level and premature coronary heart disease, or clinical atherosclerotic cardiovascular disease that requires treatment for premature coronary heart disease.

Inclisiran, the agent used in this study, is a long-acting, subcutaneously delivered, synthetic small-interfering RNA (siRNA) directed against PCSK9. The siRNA approach uses the natural RNA interference pathway by binding to the RNA-induced silencing complex, enabling it to specifically cleave mRNA molecules encoding PCSK9. A single siRNA-bound RNA-induced silencing complex is catalytic and cleaves many transcripts. This characteristic is thought to be particularly important when used in conjunction with statins, which are known to upregulate the production of PCSK9. Inclisiran is conjugated to triantennary N-acetylgalactosamine carbohydrates, which bind to asialoglycoprotein receptors on hepatocytes, leading to the uptake of inclisiran and suppression of hepatic PCSK9 production. This phase 1 study was designed so that the participants received either single- or multiple-dose inclisiran versus placebo. In the multiple-dose study, some participants were also given statins in combination with inclisiran. Plasma PCSK9 levels were lowered by inclisiran in a dose-dependent fashion, reaching a peak reduction of ≥74% at a dose of ≥300 mg at day 84 after the single-dose administration and remained significantly lowered (≥50% reduction) at day 180. Multiple-dose inclisiran administration caused a peak reduction of ≥83% at 500 mg, with or without statins and lasted up to day 196 after the first dose. LDL-C levels were substantially reduced in both the single-dose and multiple-dose groups, with peak reduction of ≥50% in the single-dose and ≥60% in the multiple-dose regimen at day 84. Most importantly, the marked reduction of LDL-C persisted for ≤180 days after receipt of the first dose, paralleling the reduction of plasma PCSK9 levels. Thus, inclisiran treatment has the potential to provide effective management of hypercholesterolemia with administration every 3 to 6 months, as compared with once or twice monthly regimens for the currently approved antibodies.

The effectiveness and durability of this RNA interference therapeutic approach is based on 4 key elements. First, the N-acetylgalactosamine carbohydrates conjugated inclisiran is highly efficient in silencing PCSK9 mRNA once delivered into the cell. Second, inclisiran primarily targets PCSK9 in hepatocytes, the main source of PCSK9. Third, the long-term, sustained reduction of PCSK9 and LDL-C reflects chemical modifications in the synthesis of inclisiran that improve molecular stability. These modifications include a combination of phosphorothioate, 2′-O-methyl nucleotide, and 2′-fluoro nucleotide modifications that improve the resistance to attack by various nucleotide-modifying enzymes. Fourth, attaching 3 N-acetylgalactosamine carbohydrates molecules to the 3′ terminus of the siRNA by means of a triantennary spacer substantially increases the affinity of the ligand to asialoglycoprotein receptor, a molecule highly expressed in hepatocytes.
Figure. PCSK9 (proprotein convertase subtilisin/kexin type 9) is primarily produced from hepatocytes and some may come from extrahepatic tissues such as small intestine and kidney. PCSK9 binds low-density lipoprotein receptor (LDLR), promoting its degradation and reducing its recycling. N-acetyl/galactosamine carbohydrate (GalNAc)–conjugated PCSK9 small-interfering RNAs (siRNAs) are efficiently and selectively delivered into hepatocytes, via asialoglycoprotein receptor (ASGPR), which is highly expressed in hepatocytes. Once in the cell, PCSK9 siRNA efficiently mediates PCSK9 mRNA degradation via the RNA interference mechanism and selectively reduces hepatic but not other tissue PCSK9 production. PCSK9 monoclonal antibodies (mAbs) bind PCSK9 in circulation regardless of its original source and block its binding to LDLR. As a result, hepatic LDLR levels are increased by PCSK9 siRNA or PCSK9 mAbs, and plasma LDL levels are decreased. Thick arrows indicate the direction of the effects.

Disclosures
A.R. Tall has served as a consultant to Amgen and Alnylam.

References


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