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Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibition and the Future of Lipid Lowering Therapy

*Lee Joseph, Jennifer G. Robinson**

University of Iowa, Iowa City, IA, USA

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ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) reduction with statins is the cornerstone of atherosclerotic cardiovascular disease (CVD) prevention. The LDL-C lowering non-statin therapy ezetimibe also modestly reduces CVD risk when added to statin therapy. There remains a clinical need for additional LDL-C lowering agents to reduce CVD risk in patients with genetic hypercholesterolemia, statin intolerance, or who are at high risk due to clinical CVD or diabetes. In clinical trials, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition using monoclonal antibodies has demonstrated robust LDL-C lowering efficacy of 50–65% and a favorable safety profile. These agents are a promising therapeutic strategy for addressing the unmet needs for additional CVD risk reduction. Regulatory approval for PCSK9 monoclonal antibodies may occur in the near future, and additional agents for PCSK9 inhibition are under development. This review focuses on the mechanism of LDL-C reduction using PCSK9 inhibition, as well as the phase I to III clinical trials of PCSK9 inhibitors. Results of the ongoing phase III CVD outcome trials are eagerly awaited.

Background

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for 30% of global mortality.[1] Low-density lipoprotein (LDL) cholesterol (LDL-C) reduction with statin therapy is the cornerstone of CVD prevention.[2] Currently, statins are the most effective drugs available for lowering LDL-C. High intensity statins result in 50–60% LDL-C reductions on average.[3] A large meta-analysis of 174,149 subjects from 27 randomized trials by Cholesterol Treatment Trialists' Collaborators reported 21% reduction in the risk of major CVD events for every 39 mg/dL LDL-C level lowering with statin therapy, independent of the baseline LDL-C levels.[4]

Based on a rigorous systematic review of randomized trial evidence, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) blood cholesterol treatment guideline recommends statin therapy for patient groups most likely to experience a net benefit.[2] High-intensity statins are recommended for high-risk patients unless safety concerns are present, and moderate-intensity statins for patients with safety concerns for high intensity statin, and in primary prevention. Use of non-statins may be considered in high risk patients who may benefit from additional LDL-C lowering, preferably with a non-statin shown to reduce CVD events in randomized trials. To date, ezetimibe is the only non-statin found to reduce CVD events when added to statin therapy in high risk patients.[5] The American Diabetes Association

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* Address reprint requests to Jennifer G. Robinson, MD, MPH, Professor, Departments of Epidemiology & Medicine, Director, Prevention Intervention Center, Department of Epidemiology, College of Public Health, University of Iowa, 145 N Riverside Drive S455 CPHB, Iowa City, IA 52242-2007.

E-mail address: Jennifer-g-robinson@uiowa.edu (J.G. Robinson).

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Abbreviations and Acronyms

ACC/AHA = American College of Cardiology/American Heart Association

AEs = adverse events

Apo A = apolipoprotein A

Apo B = apolipoprotein B

CVD = cardiovascular disease

FH = familial hypercholesterolemia

HDL = high-density lipoprotein

HDL-C = HDL-cholesterol

HeFH = heterozygous FH

LDL = low-density lipoprotein

LDL-C = LDL cholesterol

LDL R = LDL receptors

mAbs = monoclonal antibodies

MI = myocardial infarction

PCSK9 = proprotein convertase subtilisin/kexin type 9

SREBP-2 = sterol regulatory element-binding protein 2

TEAEs = treatment emergent AEs

TGs = triglycerides

recently released similar recommendations focused on statin-intensity and level of risk, as has the United Kingdom National Institute for Health and Care Excellence.[6,7]

A number of other guidelines based on expert consensus continue to recommend treatment targeting LDL-C levels or percentage reduction in LDL-C level, with the level determined by the degree of CVD risk.[8,9] However, accumulating data suggest that the risk-based approach recommended in the 2013 ACC/AHA cholesterol guideline would more appropriately treat high risk patients and prevent more CVD events than earlier approaches based on LDL-C level.[10–12] Indeed, there appears to be no lower LDL-C limit to the reduction in CVD events or atherosclerotic regression with statin therapy, suggesting more aggressive LDL-C lowering beyond LDL-C thresholds <100 or <70 mg/dl could further reduce CVD risk.[13,14]

The currently available LDL-C lowering agents for management of blood cholesterol to reduce CVD risk have several limitations, including statin intolerance, the need for additional LDL-C lowering in patients with genetic hypercholesterolemia, the inability to achieve the anticipated reduction in LDL-C cholesterol or lipid goals in some patients, and safety and tolerability concerns with non-statins other than ezetimibe. Statin intolerance is commonly encountered in lipid management. Muscle symptoms are commonly reported by patients taking statins, with up to 10–30% patients reporting muscle symptoms in observational studies.[15] However, rates are much lower in double-blind placebo-controlled trials and many patients can tolerate a statin on re-challenge.[16,17]

For high-risk patients who have suboptimal LDL-C control, patients with genetic hypercholesterolemia, and statin intolerant patients who have an indication for statin therapy, non-statin lipid lowering therapy is reasonable per the 2013 AHA/ACC guidelines. With the exception of ezetimibe in the recently reported IMPROVE-IT trial, adequately powered trials have not overall found incremental CVD risk reduction from adding niacin or fenofibrate to statin therapy, and have found evidence of excess harm with niacin.[18–20] Notably, despite the optimal treatment with currently available therapies, 70–80% remain at high CVD risk and may benefit from additional LDL-C lowering.[21–23] LDL-C reduction by means of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition is a promising novel therapeutic strategy. The PCSK9 monoclonal antibodies (mAbs) under development have generated tremendous interest due to their remarkable LDL-C lowering efficacy and favorable safety profile in clinical trials to date. This review focuses on the mechanism of LDL-C reduction from PCSK9 inhibition, as well as the phase I to III clinical trials of PCSK9 inhibitors.

PCSK9

In 2003, genetic studies identified two gain-of-function mutations in the PCSK9 gene in a French family as a cause for autosomal dominant familial hypercholesterolemia (FH), a condition associated with premature CVD and death.[24] This was the third autosomal dominant mutation for FH, in addition to mutations in the LDL receptor (LDL-R) and apolipoprotein B (ApoB) genes. The precise role of PCSK9 (initially known as NARC-1) in cholesterol regulation was subsequently elucidated in animal studies.[25]

Structure

PCSK9 is a secreted enzymatic protein of the subtilisin family of serine proteases.[26] It is primarily synthesized in the liver, but is also found in the intestine and kidney.[27] Pro-PCSK9, the 692-amino acid and 75 kDa precursor of PCSK9, consists of a pro-domain, catalytic domain, C-terminal domain and a signal sequence. It is produced in the endoplasmic reticulum, modified in the Golgi apparatus, where it undergoes autocatalytic cleavage to enter the secretory pathway, and is then released into the circulation.

Role of PCSK9 in cholesterol homeostasis regulation

The majority of LDL particles are removed from the circulation via the hepatic transmembrane LDL-R (Fig 1).[28,29] LDL-R binds to a single LDL particle and the complex is then internalized via endocytosis. Due to a drop in pH in the vesicle, the complex of LDL-R and the LDL particle dissociates, freeing the LDL-R to be recycled to the cell membrane to repeat the cycle. Each LDL-R is recycled up to 150 times. The LDL particle is degraded within the lysosome to release cholesterol for either storage or other cellular activities.

Regulation of the hepatic LDL-R activity is performed by sterol regulatory element-binding protein 2 (SREBP-2) during transcription and by PCSK9 post transcriptionally (Fig 1).[30] PCSK9 down-regulates the LDL-R expression on the hepatocyte surface by directly and irreversibly binding with the LDL-R/LDL complex.[31] The larger complex is internalized and degraded by the lysosome, resulting in subsequent degradation of the LDL-R. As a result, LDL-C clearance is decreased, leading to increased plasma LDL levels.