

## Targeting Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9): A New Promising Approach for the Management of Hypercholesterolemia

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Statins remain the standard of care for low-density lipoprotein cholesterol (LDL-C) lowering and reduction of cardiovascular risk. However, there are still cases in which patients fail to achieve the desired LDL-C goals or are intolerant to statins due to side effects (mostly myalgias). Thus, extensive research is being conducted to identify new LDL-C lowering drugs with a favorable side effect profile, which (used alone or in combination with statin therapy) would be able to produce significant LDL-C reductions and decrease cardiovascular risk [1,2].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease, which is expressed mainly in the liver but may also be found in the intestine and kidneys. The human PCSK9 gene is located in the human chromosome 1p32.3 and encodes a 692-amino acid inactive glycoprotein, which undergoes an intramolecular self-catalytic cleavage in the endoplasmic reticulum [3]. PCSK9 binds to the LDL receptors and targets the receptors for lysosomal degradation, thereby reducing their recycling and decreasing the removal rate of circulating LDL-C [4-8]. Genetic studies have shown that gain-of-function mutations of PCSK9 in humans are associated with increased LDL-C levels and increased risk for coronary heart disease [9,10], while loss-of-function mutations of PCSK9 lead to low levels of LDL-C and decreased cardiovascular risk [11]. Ironically, there is evidence that statins upregulate PCSK9 in a dose-dependent manner, which may result in attenuation of their lipid-lowering effect [12].

Several therapeutic strategies have been developed to decrease levels of circulating PCSK9, including inhibition of its self-cleavage to an active form, enhancement of its cleavage by furin, and impedance of its binding with the LDL receptor [13]. However, up to date, monoclonal antibodies are the only approved agents associated with a remarkable reduction in the levels of LDL-C and other apoB-containing lipoproteins, such as lipoprotein (a) [14,15].

Evolocumab and alirocumab are human monoclonal antibodies directed against PCSK9, which have been recently approved by the FDA as an add-on treatment to diet and maximally tolerated dose of statins for patients with familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional LDL-C-lowering.

Several studies have evaluated evolocumab. The Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1 (OSLER-1) and 2 (OSLER-2) revealed that after 12 weeks of therapy evolocumab, compared to standard therapy, reduced the LDL-C level by 61%, and this effect remained consistent over time [16].

In the Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) trial, inhibition of PCSK9 with evolocumab, administered on a background of statin therapy over an average follow-up period of 2.2 years, reduced the primary outcome (composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospital admission for unstable angina) by 15% and the key secondary outcome (composite of cardiovascular death, myocardial infarction, or stroke) by 20%. The effect appeared also to increase over time. There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were somewhat more common with evolocumab [17].

In the Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial, alirocumab, administered on top of maximally tolerated dose of statin, alone or in combination with other lipid-lowering agents, caused an additional 61.9% reduction in LDL-C levels, as compared with placebo [18,19].

The results of a large, ongoing outcome trial with alirocumab (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) [20] will likely be available in the first quarter of 2018 and are expected to provide vital information regarding the clinical benefits of alirocumab in reduction of cardiovascular risk.

Apart from the monoclonal antibodies directed against PCSK9, several other therapeutic strategies targeting PCSK9 are in development currently with very promising initial results. Small interfering RNA (siRNA) is a class of double-stranded RNA molecules, 20–25 base pairs in length, which interfere with the expression of specific genes with complementary nucleotide sequences by causing degradation of mRNA post-transcription and thus preventing translation [21].

Inclisiran is an investigational, chemically synthesized siRNA molecule, which has been shown to produce sustained hepatocyte-specific, PCSK9-specific RNA silencing. In the ORION-1 Phase 2 trial, at 180 days after administration, a single dose of inclisiran 500 mg decreased the blood PCSK9 levels by 59.3%, LDL-C levels by 41.9%, and total cholesterol levels by 26.6%. Inclisiran was well tolerated with similar numbers and proportions of adverse events reported in the inclisiran and placebo arms [22].

An active immunization against the body's own PCSK9 (AT04A vaccine) was tested for its efficacy in APOE\*3Leiden.CETP transgenic mice. The AT04A vaccine induced high and persistent antibody levels against PCSK9, causing a significant reduction in plasma total cholesterol by 53% and a reduction in the levels of LDL-C, as compared with controls. Plasma inflammatory markers, such as serum amyloid A, macrophage inflammatory protein-1 $\beta$ , macrophage-derived chemokine, cytokine stem cell factor, and vascular endothelial growth factor A, were also significantly decreased in AT04A-treated mice. As a consequence, treatment with the AT04A vaccine resulted in a decrease in atherosclerotic lesion area by 64%, a decrease in aortic inflammation, as well as in an increase of the lesion-free aortic segments by 119%, as compared with control [23].

Other potential future strategies targeting PCSK9 may include small molecule inhibitors that disrupt the processing of PCSK9, as well as the use of adnectins, which prevent binding of PCSK9 to the LDL receptor [24].

From the above review of the clinical and scientific data, it becomes apparent that interventions targeting PCSK9 by reducing its expression is a new very promising approach for the management of hypercholesterolemia and may lead to significant reductions of cardiovascular risk.

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