

## Recent Advances in Therapeutic Approaches for Familial Hypercholesterolemia

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### Abstract

Familial Hypercholesterolemia (FH) is an inherited autosomal genetic disorder characterized by elevated level of plasma low density lipoprotein cholesterol (LDLc), this condition increases the risk of early atherosclerosis and coronary heart disease. Loss of function mutation in *LDLR* and *APOB* gene leads to this condition where *LDLR* possess large number of variations that contribute to the disorder. Gain of function mutations in *proprotein convertase subtilisin/kexin type 9 (PCSK9)* gene is another cause of FH. The permanent cure for FH is not found so far, but there are several following approaches to treat FH. Use of Statins were highly recommended for the patients to treat hypercholesterolemia during the past two decades. Although the statins have significant effect on reducing cholesterol levels in the patients, it comes with other possible side effects and complexities. Targeting of PCSK9 is the novel strategy developed recently to control the plasma LDL cholesterol levels. First, inhibition of PCSK9 binding to LDL receptor by monoclonal antibodies (alirocumab and evolocumab). Second, silencing of PCSK9 gene in the liver cells mediated by RNA mediated interference (RNAi). The recent advancements in the therapeutic aspects of FH are discussed in this review.

**Keywords:** Familial hypercholesterolemia; PCSK9; LDL receptor; Monoclonal antibodies; RNAi

### Introduction

Familial Hypercholesterolemia (FH) is an inherited autosomal dominant genetic disorder of lipid metabolism which is characterized by extremely elevated levels of cholesterol in the blood plasma [1]. High concentration of LDL cholesterol is associated with atherosclerotic cardiovascular disease, mainly coronary heart disease (CHD) [2]. LDL receptor (LDLR) clears plasma LDL cholesterol from blood by endocytosis and intracellular degradation. About 85% of FH are caused by mutation or deletion in plasma membrane LDLR. Less than 10% of FH are caused by mutation in LDLR ligand or Apolipo protein B-100 (ApoB-100). Very rare type of mutation leading to FH is caused by member of proprotein convertase family

called as proprotein convertase subtilisin/kexin type 9 (*PCSK9*) [3].

Human *PCSK9* gene is located on chromosome 1p32.3 encodes for 692-amino acid inactive glycoprotein. Matured PCSK9 protein is secreted and exported to plasma membrane. It is mainly involved in differentiation of cortical neurons [4]. It is also involved in the degradation of LDLR-LDLc complex via endocytosis in lysosome and hence involved in regulating the levels of LDLR in turn the LDL cholesterol levels in the plasma [5].

Mutations in *PCSK9* gene can be either loss of function or gain of function mutation. Loss of function mutation in *PCSK9* gene leads to high LDL receptors on plasma

membrane and thus, low LDL in blood. Whereas, gain of function mutation causes low level of LDLR and thus, high LDL cholesterol. This high level of LDL cholesterol corresponds to cause FH. The gain of function mutation of PCSK9 concept was exploited for the novel therapeutic approach. Targeting the *PCSK9* gene in FH cases is a new approach to lower levels of LDL cholesterol levels. PCSK9 can be prevented from binding with LDL receptor either by decreasing the synthesis of PCSK9 with antisense or RNA interference techniques or by inhibition of PCSK9 activity with monoclonal antibodies [6].

Statins are mostly used lipid lowering drugs which inhibits cholesterol synthesis by inhibiting HMG CoA reductase enzyme. Low concentration of sterols activates the transcription factor sterol-responsive element binding protein 2 (SREBP2) [7]. Activated SREBP2 upregulates the expression of both LDL receptor and PCSK9 protein. This effect caused by statin is called as paradoxical effect of statin therapy [8]. In this approach, the over expression of PCSK9 also becomes a disadvantage of this treatment, since PCSK9 again reduces the LDLR levels. Hence, there was an urge for seeking alternate therapeutic strategies. But researchers wanted to use the statins in the advanced therapeutics in combination with PCSK9 antibodies to increase the efficiency of the treatment.

Combination therapy of statin along with monoclonal antibodies to PCSK9 protein leads to increased LDL receptors and thus decreases plasma LDL cholesterol significantly [9]. These mAbs lowers LDL cholesterol levels alone or with combination of statins. There are three known monoclonal antibodies for human PCSK9 protein – alirocumab (REGN727/SAR236553), evolocumab (AMG145) and RN316/PF04950615 developed by Sanofi/Regeneron, Amgen and Pfizer/Rinat respectively.

In phase I trials, these mAbs lowered LDL cholesterol within 2-4 weeks with or without intake of statin. In phase II trials, the efficacy of these antibodies was evaluated at week 12 [10,11]. Human mAbs inhibiting PCSK9 are effective in lowering LDL cholesterol. They are safe and well tolerated with fewer side effects than maximum statin doses. The use of PCSK9 inhibitors along with low statin dose is useful even for patients with high triglycerides and low HDL cholesterol.

Despite of statin therapy, alone or in combination, large proportion of high risk patients continued to have high LDL cholesterol levels [12]. Thus, recently investigated safe mechanism to silence PCSK9 is the use of RNAi drugs [13].

siRNA mediated in-vivo silencing of *PCSK9* confirms the reduction of *PCSK9* transcript with up to 60% reduction in plasma cholesterol concentration [14]. *PCSK9* siRNAs can be delivered to liver using lipidoid nanoparticle formulation. Formulated *PCSK9* siRNAs shows highly significant, acute, specific, and durable reduction of plasma LDL cholesterol and PCSK9 protein levels but has no effect on HDL cholesterol [15].

The effect of PCSK9 silencing lasted for 2 months after single dose administration in Nonhuman Primates (NHP) [16]. Thus, LDL cholesterol levels in humans can be decreased specifically by targeting PCSK9 with RNAi therapeutics. Inclisiran is a synthetic siRNA molecule that specifically silence PCSK9. In phase 1 trials, no serious adverse events were observed with single or multiple doses of inclisiran 84 days after administration [17]. In phase 2 ORION-1 trials, inclisiran showed significant reduction in LDL cholesterol levels at 180 days despite receiving the maximum possible dose of statin therapy [18].

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