Review Article

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PCSK 9 Inhibtors: New Era in Dyslipidemia Management

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Abstract

Low-density lipoprotein cholesterol (LDL-C) is the most important risk factor for developing coronary artery disease (CAD) as evidenced in landmark INTERHEART study. PCSK9 inhibition offers a novel therapeutic mechanism for lowering low-density lipoprotein cholesterol (LDL-C) levels.PCSK9 is a serine protease that binds the LDL receptor (LDL-R) and acts as a chaperone for endocytosis and shuttling the PCSK9-LDLR complex to lysosomes for degradation. *In the absence of PCSK9 the LDLR-LDL-C complex dissociates and LDL-R is recycled back to the cell surface.* Humanized monoclonal antibodies against PCSK 9 (*evolocumab, alirocumab, bocolicumab*) have been developed which increase LDL-R by 2-fold and lower LDL-C by up to 75 percent with no significant side effects, with the exception of injection site reactions. These novel agents play a pomising role in filling the therapeutic gap in *statin intolerant, difficult dyslipidemics and familial hypercholesterolemic patients*. When combined with statins they bring out a better cardiovascular outcome with a stable and target lipid profile.

Keywords: PCSK9 Inhibitor; Coronary Artery Disease; Low-Density Lipoprotein Cholesterol; Cardiovascular; Dyslipidemia; Statin.

Introduction

Today's dyslipidemia management revolves around the statin world. Statins although display penopoly of cardiovascular benefits through pleiotropic actions, controversy that emerged about statins include statin induced DM, statin hepatomyopathy and intolerance; those led the science emerge with those PCSK 9 inhibitors with better edge than of statins. Familial hypercholesterolemia was a big challenge to the lipidogists in achieving the goal with statin therapy but these golden drugs made the path mistfree. French people were dying of PCSK 9 mutation (F216L, R 218S) induced malignant hypercholesterolemia and accelerated early CAD where statins were not being able to achieve the lipid goal [1, 2]. Mean LDL-C level was more than 200mg/dl in those patients with PCSK 9 mutations [3]. This novel molecule was discovered in 2003 and it exhibited its promising antilipidemic efficacy in 2009 in patients with familial hypercholesterolemia. PCSK 9 mutation was associated with early onset myocardial infarction with an odds ratio of 0.40[4] while loss of function PCSK 9 mutations leads to drastically low level of LDL C in the range of 15-20mg/dl. The discovery of PCSK 9 inhibitors was a miraculous achievement in treating difficult dyslipiemics including the patients with familial hypercholesterolemia.

PCSK 9

The discovery of *proprotein convertase subtilisin/kexin* Type 9 (PCSK9) has opened the possibility for effective and adjunctive therapy for those who are not optimized with statins, who are intolerant and have little alternatives. It was initially identified as neural apoptosis-regulated convertase-1 (NARC-1). PCSK9 is processed in the endoplasmic reticulum where it undergoes cleavage producing a prodomain and catalytic subunit. In the extracellular space, PCSK9 binds to LDL receptor via its catalytic subunit while its C-terminal subunit acts as a chaperone for

endocytosis and shuttling the PCSK9-LDLR-LDL complex to lysosomes for degradation. In the absence of PCSK9, LDLR-LDL complex dissociates and LDLR is recycled back to the cell surface[5].

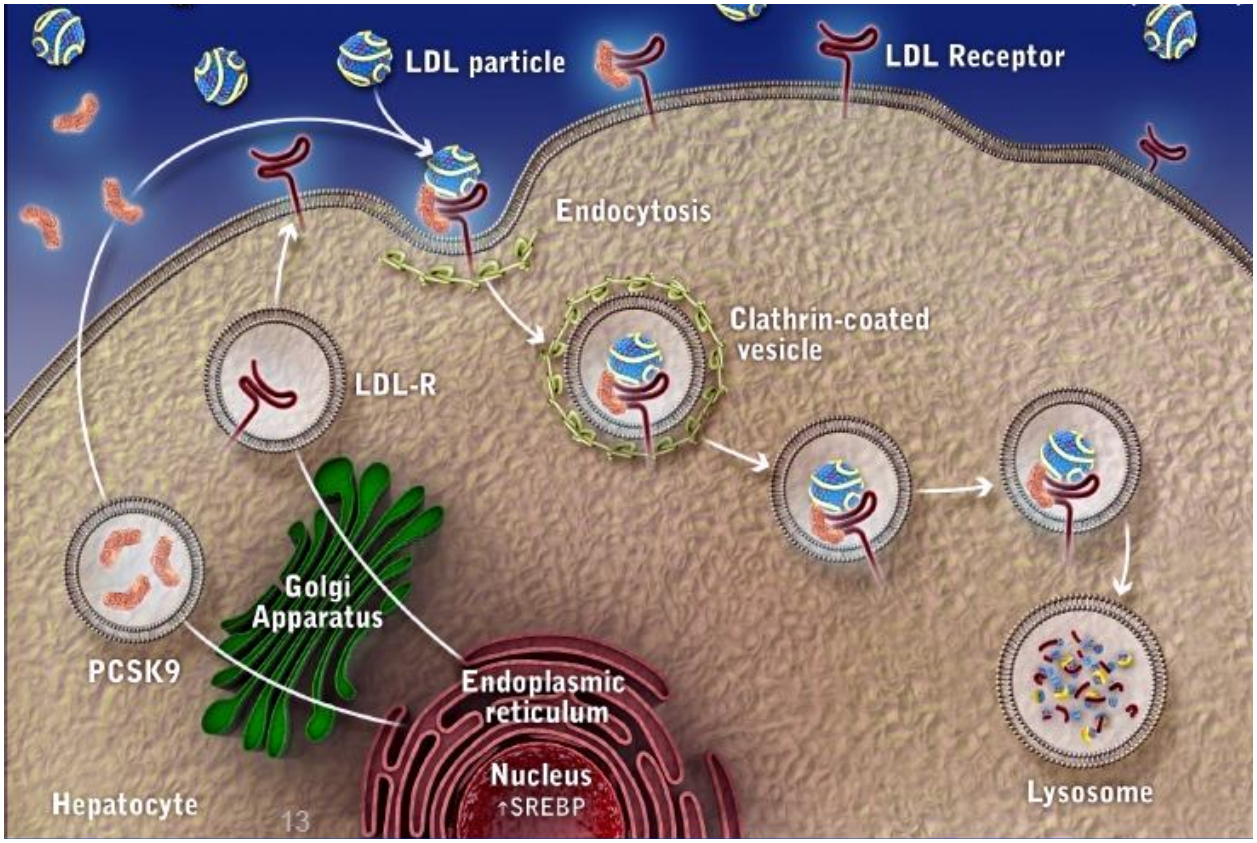

Fig. 1: PCSK 9 aiding in LDL receptor internalization

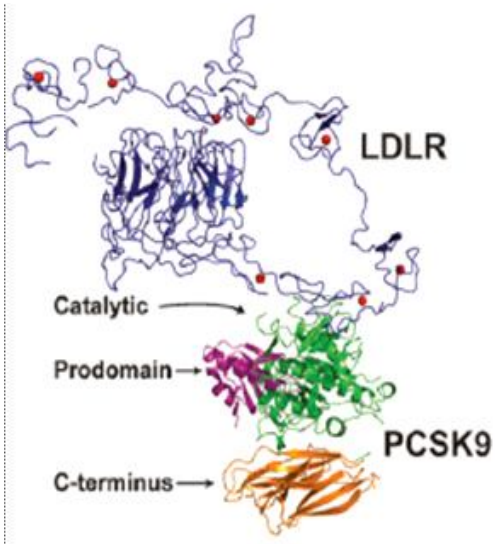

Fig. 2: PCSK 9 and LDL receptor interaction

The PCSK9 gene is located on chromosome 1p32 and its expression is regulated by intracellular cholesterol via SREBP-2[6]. Synthesis of PCSK9 occurs mostly in the liver, small intestine and kidney. Low intracellular levels of cholesterol stimulate the synthesis of LDL-R and PCSK9 to maintain intracellular delivery of cholesterol. *In the setting of statin, fibrate and ezetimibe use, PCSK9 expression is up-regulated due to low intracellular cholesterol levels* [7]. Thus, *PCSK9 inhibition is additive to statin therapy and play a synergistic role in lipid-lowering effect.*

Familial Hypercholesterolemia and Pcsk 9

Heterozygous FH is an autosomal dominant genetic disorder with an estimated prevalence between 1 / 200and 1 / 500 in the general population It is estimated that PCSK9 mutations represent 1% to 2% of all familial hypercholesterolaemia (FH) cases. Mutations of the PCSK9 gene are the third cause of FH, after mutations in the LDL receptor or apolipoprotein B (ApoB) genes.

Pcsk 9 Inhibitors

Approach to reduce PCSK 9 interaction with LDL receptor includes inhibition by monoclonal antibodies and *adnectins* and reduces PCSK 9 synthesis by *antisensen* RNA. Monoclonal antibodies evolved from mouse monoclonal antibody to chimeric, humanized and human monoclonal antibody in due course of time.

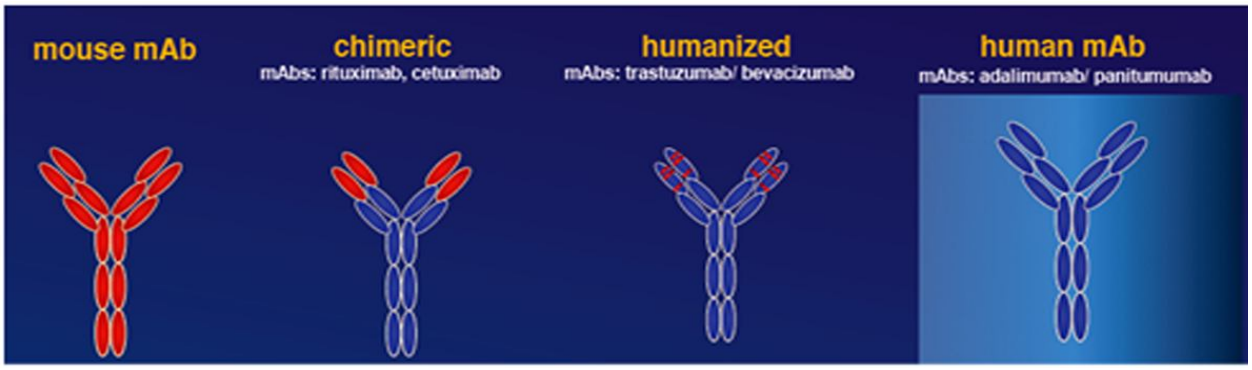

Fig. 3: Evolution of monoclonal antibody

Monoclonal Antibodies

In 2009, the first successful development of monoclonal antibody against PCSK9 was developed by Chan et al [8]. The fully human monoclonal antibody (mAB) binds to both the catalytic and prodomain sites preventing PCSK9 binding to LDL-R. Monoclonal AB increase LDL receptor levels by 1.7-2.2-fold and had synergistic effects when administered concomitantly with statin.

Alirocumab

Alirocumab shows dose-dependent LDL-C lowering effects. In the phase II clinical trial evaluating the use of alirocumab in the background of atorvastatin in subjects with LDL-C e 100 mg, arilocumab decreased LDL-C by as much as 72 % with *150 mg administered every two weeks*[9]. With significant reduction in apolipoprotein B (apoB), non-high density lipoprotein cholesterol (non-HDL-C) and lipoprotein (a) [Lp(a)][10]. Alirocumab is well-tolerated and effective in FH (68 % reduction in LDL-C compared with 11 % in the placebo group)[11]. In the ODYSSEY program presented in European Society of Cardiology (ESC) congress, alirocumab was shown to decrease LDL-C levels by 61 % compared to placebo and also lowered CV risk after one year therapy (HR 0.46, CI 0.26-0.82, p = <0.01) (*ESC Barcelona Spain 2014*).

Evolocumab

Evolocumab, a full human monoclonal antibody, is administered subcutaneously either as every two weeks or every four weeks dosing regimen. GAUSS study evaluated the efficacy and safety of evolocumab in patients with statin intolerance with significant reduction in LDL-C compared to placebo (41%) [12]. When administered to subjects who are already taking statin, administration of evolocumab further decreased LDL-C by *63–75 %* compared to placebo in subjects with heterozygous FH [13]. Evolocumab also decreased Lp(a). In a small study by Stein et al., the effect of evolocumab was studied in both LDL-R negative subjects and LDL-R defective patients. Evolocumab significantly reduced LDL-C by 26 % in only the LDL-R defective subjects. In a 12-week phase III clinical trial, evolocumab with moderate or high-intensity statin showed significant reduction in LDL-C (up to 75 % reduction)[14]. Also in another 12-week phase III study evaluating evolocumab use in subjects with intolerance to statin, those treated with evolocumab had significant reduction of LDL-C compared to ezetimibe (53–56 % vs 37–39 % p< 0.001). Patients those were previously enrolled in prior phase II studies (GAUSS, RUTHERFORD, LAPLACE-TIMI 57, and MENDEL) were evaluated in the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) trial. This study showed that *subjects who continued to take evolocumab for the duration of the year on a monthly dosing regimen, maintained decreased LDL-C levels, whereas those that discontinued the study drug resumed their baseline levels* [15]. In the LAPLACE-TIMI 57 phase II trial, the mean LDL-C concentration reduction was dose-dependent, and ranging from 41.8% to 66.1% every two weeks, and from 41.8% to 50.3% every four weeks. In the MENDEL trial, evolocumab in 406 patients with hypercholesterolaemia and statin intolerance significantly reduced LDL-C concentrations with the maximal effect for the regimen of 140 mg every two weeks (–51%).

In the RUTHERFORD trial, 167 patients with heterozygous familial hypercholesterolemia and uncontrolled LDLC (e 2.6 mmol/l) with statin and evolocumab achieved substantial reduction in LDL-C (43% for 350 mg and 55% for 420 mg) on top of intensive statin use. Recently, the DESCARTES trial, including 901 patients with a range of cardiovascular risks treated with diet ,atorvastatin 80 mg plus ezetimibe once a day were randomised to 420 mg evolocumab or placebo every four weeks. At 52 weeks, evolocumab significantly reduced LDL-C

levels with all previous described regimens (from 48.5% to 61.6%), as well as apo B, non-high-density lipoprotein cholesterol and lipoprotein. The most common adverse events were nasopharyngitis, upper respiratory tract infection, influenza and back pain.

Bococizumab

The monoclonal antibody bococizumab has undergone phase I clinical trial and shown that single and escalating intravenous and subcutaneous dose significantly lowered LDL-C by as much as 54 % with 150 mg Q2 week regimen without significant adverse effects[16].

Other Targets for Pcsk9 Inhibition

Direct inhibition of PCSK9 can be attained using small mimetic peptides called *adnectins*. Mimetic peptides of the PCSK9 binding domain for LDL have been shown to decrease LDL-R degradation[17]. Another approach in PCSK9 inhibition is gene silencing techniques. Antisense RNAs (siRNA) are also being developed to target PCSK9 mRNA. Natural inhibitors, such as annexin A2, a protein expressed in many tissues, inhibit PCSK9 and increase LDL-R.[18] *Berberine,* a natural occurring plant alkaloid has been shown to also decrease PCSK9 mRNA expression and increase LDL-R *in vitro* and animal studies.[19]

Monoclonal Antibody Dose and Ldl-C Reduction

All monoclonal antibodies produce dose dependent LDL-C reduction ranging from 48-85% as depicted in the following table.

Pcsk 9 and Cariovascular Outcome

Metaanalytic cardiovascular benefits of PCSK 9 inhibitors are depicted below providing the message that PCSK 9 inhibitors are associated with a better CV outcome.

Table 1: Dose dependent LDL-C reduction with monoclonal antibody

Monoclonal Antibodies	Reduction of LDL-C from Baseline
Alirocumab	
150 mg every two weeks	66–72 %
300 mg every four weeks	43–48 %
Evolocumab	
140 mg every two weeks	51–76 %
420 mg every four weeks	48–71 %
Bococizumab	
150 mg every two weeks	33 % (0.5 mg/kg) – 85 % (18 mg/kg)
300 mg every four weeks	Mean reduction 53 mg/dL
	Mean reduction 45 mg/dL

low-density lipoprotein cholesterol

Table 2: PCSK 9 inhibitors and CV outcome

Outcome	OR (95% CI)	P	I^2	N	Events PCSK9 group (%)	Events control group (%)
All-cause mortality	0.45 (0.23-0.86)	0.015	0%	10,159	19 (0.3%)	21 (0.5%)
CVD Mortality	0.50 (0.23-1.10)	0.084	0%	10,159	12 (0.2%)	13 (0.3%)
MI	0.49 (0.26-0.93)	0.030	0%	5,195	19 (0.6%)	19 (1.0%)

Phase Iii Study and Monoclonal Antibody

Adverse Events

Serious adverse events from monoclonal antibodies targeting PCSK9 are rare. *The most common adverse reactions are local injection site reactions* (erythema, pruritis, discoloration, haematoma, swelling). In the GAUSS trial, myalgias were the most common adverse event but had low incidence overall [20]. Alirocumab had similar adverse reactions between placebo and treatment groups in its phase II trials. In a dose escalating study of alirocumab, one of 152 subjects receiving a dose of alirocumab developed *cutaneous leukocytoclastic vasculitis* that was successfully treated with prednisone[21]. For evolocumab, the most common treatment related adverse reaction was not only injection site reaction (pain), but also headache [22].

Table 3: Phase III study with monoclonal antibodies

Monoclonal Antibody	Name of Phase III	Population
Evolocumab	MENDEL-2	Subjects with hypercholesterolaemia, Framingham Risk score < 10%, monotherapy
		Statin-intolerant subjects, compared to ezetimibe
	GAUSS-2	Subjects with hypercholesterolaemia, statin intolerance, ezetimibe controlled
	LAPLACE-2	Subjects treated with evolocumab on high or low dose statin
	FOURIER	Evaluating cardiovascular outcomes in subjects with hypercholesterolaemia and elevated risk cardiovascular risk
Alirocumab	ODYSSEY	Global Phase III program
	COMBO-I	subjects treated with maximally tolerated statin therapy
	CHOICE I	Alirocumab administered every four weeks compared with placebo
	CHOICE II	Alirocumab as monotherapy compared to other non-statin lipid lowering therapies
	LONG TERM	Alirocumab use in the background of lipid lowering therapies and long term safety and efficacy
	OUTCOMES	Alirocumab effects in cardiovascular outcomes in subjects with acute coronary syndrome
Rocolicumab	SPIRE-1	CV outcomes in subjects with high risk and LDL-C ≤ 70 but ≤ 100 mg dL
	SPIRE-2	CV outcomes in subjects with high risk and LDL-C ≥ 100 mg dL
	SPIRE-IS	Subjects who are intolerant to statin
	SPIRE-HR	Subjects with high or very high risk for CV events
	SPIRE-LL	Subjects with primary hyperlipidaemia at high or very high risk

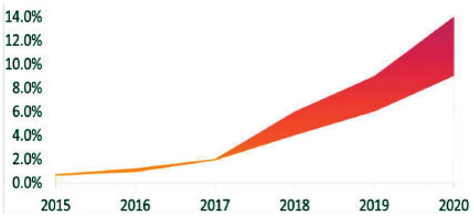

Fig. 4: Projected PCSK 9 inhibitors among Statin users (National Cooperative USA)

Conclusion

Although statins have revolutionized lipid therapy, there remains a significant residual risk among statin intolerant, inadequately controlled and patients with familial hypercholesterolemia that can be further targeted. Statin-induced myopathy may represent up to 10 % of treated patients in a primary care setting. PCSK9 inhibitors have successfully shown to rescue these situations with significant reduction in LDL-C, non-HDL-C and Lp(a). As an add on therapy to statins, those acting *synergistically* with statins will bring out significant reduction in LDL-C with better cardiovascular outcome in near future.

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