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Review Article

Positioning of PCSK9 Inhibitors in hypercholesterolemia

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ABSTRACT

PCSK 9 inhibitors currently have a market of 3 billion USD and by next 10 years it will raise to 13 billion USD in developed world. The rising prevalence of dyslipidemia and other lipid disorders are linked to lipid metabolism due to an unbalanced lifestyle and rising alcohol and tobacco use. PCSK9 inhibitors are injectable monoclonal antibodies that inactivate PCSK9 receptors. PCSK9 inhibition decreases degradation of the LDL receptor, thus raising the number of functioning LDL receptors on hepatocytes and lowering the number of LDL particles in the blood, which are atherogenic. For patients with very high cardiovascular risk, PCSK9 inhibitors and ezetimibe are added to statins, where they significantly lower absolute risk for myocardial infarction (MI) and stroke. Statins are known to upregulate PCSK9 encoding gene. PCSK9 inhibitors are given bimonthly or monthly and are reasonably safe. Familial Hypercholesterolemia (FH) a common inherited disorder of lipid metabolism, has mutations in one of these 3 genes: LDLR, APOB or PCSK9. These patients have 22 times more risk of coronary event than general population. Addition of a PCSK9 inhibitor to low dose statin therapy will be more effective in lowering LDL and avoiding the side effects of statins. PCSK9 inhibitors can contribute to both the stabilization and regression of atherosclerotic plaques and thereby avoid or delay major adverse cardiac events.

1. Introduction

Coronary artery disease (CAD), tends to develop when cholesterol builds up on the arterial walls, creating plaques. Cholesterol can be reduced by diet and exercise (improves HDL levels),

Cardiovascular disease becomes more evident when the cholesterol levels are raised.Tables 1 and 2 Patients are at greater risk if they have a brother or father who had a heart attack or stroke before the age of 55.[1]

1.1. Conservative measures for reducing cholesterol levels

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as statins, are recommended as first-line agents in the reduction of low-density lipoprotein cholesterol (LDL-C). The longer half-lives of rosuvastatin, atorvastatin, pitavastatin, and pravastatin allow these agents to maintain a therapeutic drug concentration over a 24-hour period. Ezetimibe is a cholesterol absorption inhibitor used to lower total cholesterol, LDL-C, Apo-B, and non-HDL-C in primary hyperlipidemia and familial hypercholesterolemia. They can be effectively combined with statins. Ezetimibe inhibits cholesterol absorption by 54%, which contributes to the net 18-20% reductions in LDL-C Omit from here, and

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Table 1: Merit anddemerit of circulating cholesterol

Advantages of Cholesterol	Disadvantages of Cholesterol
Provide cell strength and rigidity. It is. Used in membranes of each cell	Cholesterol is not soluble, thus its transported in body through lipoproteins
Raises Vitamin D in Cell.	Low density lipoproteins transport cholesterol away from liver and transports it to arterial walls, leading to atherosclerosis. (Bad Cholesterol)
Transport fat soluble vitamins A and E	High density lipoproteins – are responsible for transporting cholesterol, back in liver (Good Cholesterol)
Protects skin – involved in healing process	

Table 2: Mayo clinic directives on cholesterol levels [1]

Total Cholesterol	Comment
< 70mg/dl	People with CAD, Stents or Bypass Surgery
<100mg/dl	People at risk of coronary artery disease or who have diabetes.
100-129 mg/dL	If there is no coronary artery disease.
Triglycerides	
240-499	High
500	Very high
HDL Cholesterol	
50mg/dl women and Men 40-59mg/dl	Borderline adequate
60mg/dl	Very desirable

increases HDL-C by 2.5-5%.

The other therapies include Fibric acid derivatives (also called fibrates), Bile acid sequestrants (also called bile acid resins), Nicotinic acid (also called niacin which improved HDL-C levels) Omega-3 fatty acids are triglycerides that get broken down into smaller fatty acid units. They act to reduce plasma triglyceride levels however they increase the cholesterol levels.

Adenosine triphosphate-citrate lyase (ACL) inhibitors, work in the liver to block the production of cholesterol.eg Bempedoic acid. [2]

Muscle aches and pains are common in those taking statins, having poor muscle mass, vitamin D deficient, alcohol consumers, hypothyroid, people consuming antifungals or antidepressants or those taking grapefruit, pomelo or pomegranate juice.

2. Phrasing Statin Intolerance

This is characterized by the following features: [3,4]

Table 3: Pro and cons of statins

Advantages of Statins	Disadvantages of Statins
Reduction in LDL and Apolipoprotein B	Primary prevention benefits are unclear
Decrease Total Cholesterol	Myositis and Myalgia are common side effects
Stabilizes blood vessel lining	Concern over raised blood sugar levels more with potent statins
Plaques less likely to rupture – lowers risk of heart attack.	Memory loss, confusion
	Statins diminish pancreatic β-cell function via Ca^{2+} signaling pathways and down-regulate the insulin-responsive glucose transporter 4 (GLUT-4), raise glucose levels

1. Significant or alarming symptoms (most commonly muscle pain and/or fatigue)
2. History of marked CK elevation
3. Biomarker abnormalities attributed temporally and unequivocally to statin use
4. Intolerance to 2 statins, including one at the lowest approved starting dose

Statin intolerance would require the use of effective and alternative drugs, which can lower LDL levels satisfactory.Table 3 [5]

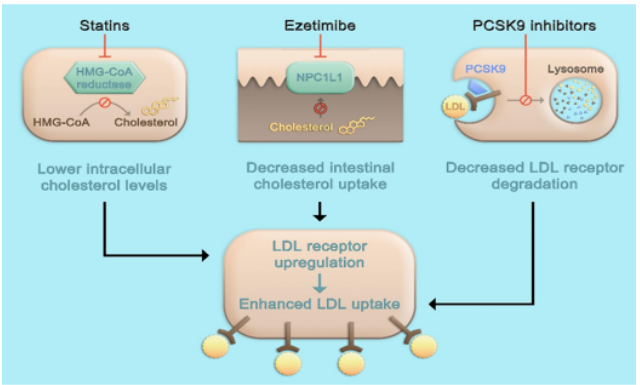

Fig. 1: Site of action of ant cholesterol drugs: [6]

Ezetimibe added to statin therapy results in an additional 15–20% reduction in LDL in this patient population. Patients receiving ezetimibe/simvastatin had statistically significant reductions in LDL-C across all doses (52–61%) rosuvastatin.

PCSK9 is a serine protease composed of 692 residues. It contains a prodomain, catalytic domain, and a histidine rich C-terminal domain. PCSK9 complex binds to the epidermal growth factor-like repeat (EGF-A) of the LDLR's EFG domain. Figure 1

PCSK9 is mainly produced in liver, kidney and small intestine. PCSK9 inhibitors are actually human monoclonal antibodies obtained from cell cultures. These antibodies have a high specificity for their PCSK9 target. [7–9]

3. Mode of Action of PCSK9 Inhibitors

PCSK9 binds to the LDLR on the surface of the hepatocyte, leading to the internalization and degradation of the LDLR in the lysosomes, and reducing the number of LDLRs on the cell surface.Table 4

Table 4: Effects of PCSK9 inhibitors showing beneficial effects

1.	LDL C Reduction: results in approximately 55% reduction in LDL-C levels.
2.	PCSK9 inhibition also decreases the plasma concentrations of lipoprotein(a), around 20–30%.
3.	HDL-C: 8% increases in HDL-C.
4.	Plaque regression: Better plaque reduction as compared to statins. Progression of atherosclerotic plaque can be halted, when LDL-C levels are reduced to below 70 mg/dl
5.	Clinical outcomes: 15% to 48% lower hazard of a composite of CV death, MI, stroke.

Atherosclerosis is a slow process with lipids accumulating in the arterial wall. LDL-cholesterol is a major driver of the process and reduction of LDL may slow down and even reverse the atherosclerosis. [10]

4. Advantages of PCSK 9 inhibitorsTable 5

1. There is no intolerance with use of these drugs, as compared to statins 68.1% - 100 % and Ezetimibe 41.6 % to 83.3 %.
2. Reduce the risk of heart attack by 27 %
3. PCSK9 inhibitors have been shown to be very effective in both heterozygous FH and homozygous FH and in patients who cannot achieve a low LDL-C despite maximal dose of statins.
4. No dose adjustment is required for mild to moderate hepatic or renal impairment [11,12]

Table 5: ADR profile of statin, Ezetimibe and PCSK9 inhibitors

Statin	Ezetimibe	PCSK9 inhibitors
Muscle pain (7-29 %), autoimmune myopathy, headache, and digestive problems	Abdominal pain and diarrhea, weakness and cramps	Limb or muscle pain {10-20 %} and tiredness and in some cases diabetes mellitus. Influenza like illness in 27.9%

PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors are safe and reduce risk of cardiovascular diseases, but their long-term safety is not clear. [13]

5. Limitations of PCSK9 inhibitors

1. Local reactions such as erythema, swelling or itching, the incidence of which ranges between 2.1% and 10.4%, since no oral formulation is available. (Oral Formulations are recently being considered).
2. PCSK9 inhibitors are very expensive compared to statins
3. Generic development is on anvil, so as to reduce therapy cost
4. Limited major medications.
5. Therapeutic effect is severely attenuated due to the development of antibodies [14,15]Tables 6, 7 and 8

A meta-analysis found evolocumab to be a more potent reducer of LDL-C than alirocumab. There were no significant differences in ADR profile between alirocumab and evolocumab. Development of Bococizumab was discontinued in 2016, due to higher incidence of side effects and development of Anti-drug antibodies in 48% of subjects at the 1-year (Spire 1 and 2 Trials).

MK-0616 (Merck), oral formulation, was generally well tolerated and reduced LDL-C across all dose levels compared to placebo, now undergoes Phase III Clinical study. The other PCSK9 Inhibitors therapies in the pipeline include LIB003, AZD8233 (ION449), Cepadacursen sodium (CIVI-007), CiVi-008.

6. The other Evolving Specific Therapies are

1. Vaccine: immunotherapy against PCSK9 using a nanoliposomal peptide-based vaccine termed L-IFPTA+ can protect against hypercholesterolemia. This is under human evaluation
2. Monobodies: Adnectins, are proteins derived from human fibronectin-10th-type III-domain and engineered for high-affinity target binding. It down regulates PCSK9 , leading to reduction of raised lipid levels. [19,20]

7. PCSK9 inhibitor resistance: This is characterized by

1. Patients having < 15 % reduction of LDL cholesterol, after 3 months of therapy
2. Dysfunction/ mutation of LDLC receptor and Apo E and Apo B

PCSK9i hypo-responsiveness are thought to occur by impaired monoclonal antibody entry into the systemic circulation.Tables 9 and 10

This is often reported sporadically in few cases. [21]

Table 6: Approved uses of PCSK 9 Inhibitors [16,17]

1.	As an adjunct to other LDL-C-lowering therapies in patients with homozygous familial hypercholesterolemia, to reduce LDL-C.
2.	Patients with side effects to statins, particularly muscle symptoms that prevent statin use or substantially limit the dose.
3.	Patients with CVD at very high risk, where LDL levels are > 70 mg/dl, where maximally tolerated dose of statin has been used.
4.	In adults with established cardiovascular disease (ASCVD) to reduce the risk of myocardial infarction, stroke, and coronary revascularization.
5.	Patients with ASCVD (Atherosclerotic Cardiovascular disease) who have LDL-C > 100 mg/dL (non–HDL-C 130 mg/dL) while on maximally tolerated statin (ezetimibe) therapy; and heterozygous hypercholesterolemia (FH) patients without ASCVD who have LDL-C >130 mg/dL (non–HDL-C >160 mg/dL) while on maximally tolerated statin (Ezetimibe) therapy.

Table 7: Comparison of newer cholesterol lowering agents [18]

Drug Class	Usage	Change in lipid parameters	CV risk reduction when used with statins
Selective cholesterol absorption inhibitor: ezetimibe- 10mg daily or used in alternate days	Primary hyperlipidemia, homozygous familial hypercholesterolemia.	22.7% incremental decrease in LDL-C when added to a statin	5.8% Relative risk reduction
PCSK9 inhibitors	Adjunct treatment: heterozygous familial hypercholesterolemia	60% incremental decrease in LDL-C	15% Relative risk reduction
Cholesteryl ester transfer protein inhibitor (CETP): Anacetrapib, Torcetrapib, Dalcetrapib, and Evacetrapib-inhibition of the CETP would raise the concentration of HDL-C and may reduce the risk of CAD.	Elevated Cholesterol levels to prevent cardiovascular disease	Anacetrapib treatment lowered Lp(a) by 34.1% & 42% decrease in LDL-C levels	15% Relative risk reduction

Table 8: Comparison of PCSK 9 Inhibitors

Drug	Evolocumab (recombinant DNA technology) – FDA , Aug 2015	Alirocumab (recombinant DNA technology) FDA , July 2015	Inclisiran (siRNA against PCSK9) FDA, December 2021 – long acting
Company	Amgen	Sanofi	Novartis
LDL-C Reduction HDL-C down	48-71% 5-10 %	43- 72% 5- 10%	50- 54% 5-10%
Total Cholesterol	-42.0	-39.0	
Triglycerides	-17.4	-9.2	
Lp(a)	-45.0	-26.8	
ApoB	-56.4	-50.2	
Specific ADR	hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or genitals	Pain at injection site , Depression , dizziness , rash , Muscle pain and soreness	hyperpigmentation, hiccough, siRNA-induced peripheral neuropathy
Dose	140 mg SubQ every 2 weeks 420 mg SubQ every month	75 mg SubQ every 2 weeks 300 mg SubQ every month	Three 300 mg SC injections during the first year (at day 1, 90, and 180) and 2 for each subsequent year
Proposed Indications	Heterozygous and homozygous familial hypercholesterolemia, atherosclerotic cardiovascular disease	Heterozygous and homozygous familial hypercholesterolemia, atherosclerotic cardiovascular disease	Heterozygous and homozygous familial hypercholesterolemia, atherosclerotic cardiovascular disease

Table 9: Landmark trials with PCSK9 inhibitors[6,22]

Drug	**Alirocumab**	**Evolocumab**
Trial name	Odyssey outcome	Fourrier
Sample size	18000	27564
Statin dosing	Higher statin dose	Atrorvastain 20mg or equivalent
Half Life	17-20 days	11-17 days
Volume of distribution (L)	0.04-0.05	3.3
Bioavailability	85 %	72%
Baseline LDL-C	70mg /dl	92mg/dl
Treated LDL-C	-Significant Reduction	-59 % at 48 weeks
Primary Endpoint	CHD, MI, Stroke, Unstable angina, Median followup – about 2.8 years	CHD, MI, Stroke, Coronary revascularization Median followup – about 2.2 years

Table 10: Group analysis of PCSK 9 inhibitors

Strength Reduction of LDL-c Significant, over period of time. Can reduce CV events significantly	Weakness Niche Indication Have to be used twice or once monthly atleast for 1-2 years, for desired reduction of cholesterol levels Patients should be injected in hospital or well maintained clinic since these are biologicals
Opportunity Can have wide promotion to interventional cardiologists and Internal Medicine	Threat Newer molecules in pipeline Future Development of Generics

7.1. Specific need for PCSK9 inhibitors

The incidence of Familial hypercholesteremia is 1: 200 or 250 persons, which has risen as compared to earlier decades. Heart attacks may occur before age 50 in men and age 60 in women. The altered gene (gene mutation) that causes familial hypercholesterolemia is located on chromosome 19. There are over 1600 known mutations of the LDLR gene. The impairment of LDL Receptor results in decreased LDL clearance from the plasma and an elevation of low-density lipoprotein cholesterol (LDL-C). Tendon xanthomas and corneal arcus senilis commonly occurs in these patients. The risk of death or coronary artery disease in relatives of patients with FH was 52% and 32% in males and females, respectively. PCSK 9 inhibitors are specific for this Indication and hence they are preferred. Other drugs are Antisense oligonucleotide to ApoB (mipomersen) and Microsomal triglyceride transfer protein (lomitapide)[23]

7.2. Natural PCSK9 inhibitors

Soy Proteins, Lupin protein, Berberine are natural products which can inhibit PCSK9 to mild degree. They also cause hypoglycemic effects. Polyphenols are plant-derived secondary metabolites found in fruits, vegetables, nuts, seeds, herbs, spices, stems and flowers, as well as in tea and red wine. PCSK9 inhibitor inhibits PCSK9 degradation of LDL-R, improving LDL-C clearance and lowering plasma LDL-C levels.[24]

8. Discussion

PCSK9 stimulates pro-inflammatory cytokines The TLR4/NF-κB is an important signaling pathway in the initiation and progression of atherosclerotic lesions through induction of vascular inflammatory responses. There is also increase in proinflammatory mediators like *TNF-α , IL-6, IL-1,* and MCP-1. PCSK9 inhibitors are the most effective lipid-lowering agents. PCSK9 inhibitors are promisingly first-line lipid-lowering treatment for patients with hypercholesterolemia, especially for those with statins intolerance or resistance or familial hypercholesterolemia. The global PCSK9 inhibitor market is growing owing to the elevated geriatric population with emerging cardiovascular diseases. PCSK9 inhibitors have an anti inflammatory benefit and have inhibitory effect on platelet aggregation, thus have benefit in Acute coronary syndrome. PCSK9 inhibition is capable of promoting a mean LDL reduction of up to 60%, as every 38 mg/dL reduction in LDL appears to be associated with a 22% reduction in cardiovascular risk. PCSK9 levels are significantly higher in T2DM without statin therapy compared with normoglycemic subjects. Even individuals with T1DM had higher PCSK9 concentrations, proving a positive correlation with hypertriglyceridemia. PCSK9 inhibitors might prove effective in other clinical conditions, which need to be further evaluated such as peripheral and carotid artery disease, acute coronary syndromes, stent restenosis, and cardiomyopathies.

PCSK9 inhibitors are not recommended as the first-line treatment for lowering LDL cholesterol in familial hypercholesterolemia. They are often taken alongside other treatments like statins, or are used when other medications or combinations used are not effective. The Fourier study, with Evolocumab it was found that women had lower LDL-C reduction compared to men after initiation of PCSK9 inhibition. In women reported side effects were higher. The pharmacovigilance databases have shown significant high

Individual Case Study Report to about 66%.

9. Latest Developments in PCSK 9 I

Oral PCSK9I (MK-0616) — is a cyclic peptide.

Injectable treatments targeting PCSK9 have demonstrated significant reductions in LDL-C levels and decreased risk of ASCVD events. An oral PCSK9 inhibitor that may achieve robust reductions in LDL-C and is well tolerated may offer potential advantages over injectable PCSK9 inhibitors in terms of ease of dosing, patient preference, and access.

MK-0616 is an orally bioavailable, renally excreted, macrocyclic peptide that binds to PCSK9 (proprotein convertase subtilisin/kexin type 9) in development for the treatment of hypercholesterolemia.

9.1. Phase 1 study[25]

Two phase one studies with a total of 100 participants (60 participants were randomized in the single and 40 in the multiple dose study) demonstrated a dose dependent increase in plasma exposure. Free plasma PCSK9 levels drop more than 90% from baseline at all dose levels. And low-density-lipoprotein cholesterol (LDL-C) levels dropped approximately 65% when MK-0616 was given daily for 2 weeks on a background of statin therapy. MK-0616 was well tolerated at doses up to 300 mg without deaths, any serious adverse events, or clinically meaningful changes in laboratory safety tests, vital signs, or ECGs.

9.2. Phase 2[26]

Phase 2b was conducted with 381 participants (49% female; median age 62 years), it was randomized, double-blind, placebo-controlled, multicenter trial aimed to evaluate the efficacy and safety of MK-0616 in participants with hypercholesterolemia.

9.3. Study design(Figure 2)

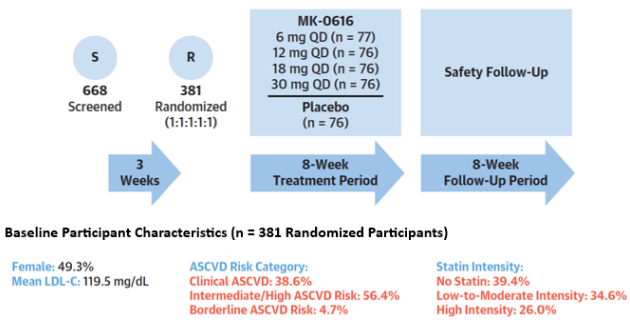

Fig. 2: A phase 2b study of an oral PCSK9 inhibitor (MK-0616): study design

9.4. Results

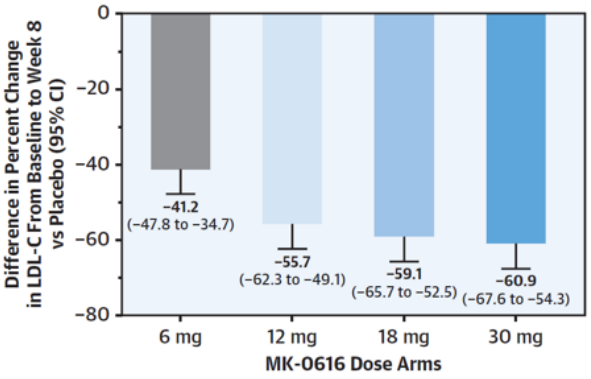

Fig. 3: Efficacy (N-380 treated patients)

All doses of MK-0616 demonstrated statistically superior reductions in LDL-C vs placebo with up to 60.9% placebo-adjusted reduction from baseline values. MK-0616 was well tolerated with no overall trends in AEs across treatment groups (Adverse events occurred in the MK-0616 groups (39.5% to 43.4%) as placebo - 44.0%).

Oral PCSK9I (MK-0616) at doses from 6 mg to 30 mg daily provided clinically meaningful reductions of LDL-C that were superior to placebo in participants with hypercholesterolemia with a wide range of ASCVD risks and background statin therapies. Further studies are required to validate efficacy and safety of MK-0616.Figure 3

10. Source of Funding

None.

11. Conflict of Interest

None.

12. Acknowledgment

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