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# Literature Review Of Alirocumab : Mechanism Of Action, Pharmacokinetics, Safety, And Clinical Outcomes

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A B S T R A K

Hyperlipidemia is an established risk factor for cardiovascular disease (CVD) development. The latest guideline on lipid management emphasizes treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) at doses proven to reduce CVD events. However, some of statin-treated patients have persistent elevation of cardiovascular risk due to inadequate control of low density lipoprotein cholesterol (LDL-C) levels. In addition, adverse effects of statins may limit their tolerability and the ability to attain effective doses in some patients. A new class of drugs that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9) has been developed to treat hyperlipidemia. PCSK9 inhibitors are monoclonal antibodies for proprotein convertase-subtilicin/kexin type 9, which, significantly reduce the concentration of LDL-C in vivo by inhibiting the degradation of LDL receptors in hepatocytes. The introduction of the PCSK9 inhibitor heralded a new era of intensive LDL-C reductions with LDL-C concentrations lowered below the rate that once thought possible with conventional treatments such as statins. On July 24, 2015, the United States Food and Drug Administration (FDA) approved Alirocumab, the first converged PCSK9 inhibitor. This review discusses the mechanisms of action, pharmacokinetics, safety and clinical outcomes of the Alirocumab.

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## 1. INTRODUCTION

Cardiovascular disease is the leading cause of global death, accounting for more than 17.9 million deaths per year in 2015, this number that is expected to grow to more than 23.6 million by 2030.[1] Many factors contribute to CVD incidence, including age, family history, obesity, lack of physical activity, diet, smoking, high blood pressure, and hyperlipidemia. Hyperlipidemia is the major risk factor in the development of CVD. Some double blind placebo controlled trials have shown that treatment with HMG-CoA reductase inhibitors (statins) lower Low-Density Lipoprotein (LDL-C) levels and reduced risk of myocardial infarction or death from coronary heart disease. [2,3]

Compared to the low-dose of statin therapy, high-dose statin therapy further lowers the levels of LDL-C and reduces the incidence rate of CVD.[3] However, the safety problems associated with high-dose statins are also in doubt, and in fact the CVD events continue to happen in some patients on Statins. Side effects including myopathy (ranging from mild to myalgia olyisis rhabdomiolisis weight) and the incidence of diabetes or worsening of diabetes can restrict the use of Statins or the ability to achieve their efficacy.[3,4] Therefore, the newer treatment modality for lowering LDL-C is needed in the clinical practice. In 2015 the Food and Drug Administration (FDA) approved a drug group that targets the novel pathway to reduce LDL-C. The drug is a monoclonal antibody that disables the proprotein convertase subtilsin-kexin type 9 (PCSK9). PCSK9 inhibitor has been reported to reduce the level of Low-density Lipoprotein Cholestrol (LDL-C) in patients who are using statins. PCSK9 inhibitor that was first approved by the FDA in 2015 is alirocumab.[5] In the phase 2 study which lasts 8 to 12 weeks, Alirocumab reduced LDL cholesterol level of 40% up to 70% when added to statin therapy. PCSK9 promotes degradation of LDL receptors, thus reducing LDL clearance from the circulation.[6] This review discusses the mechanism of action, dosing and administration, pharmacokinetics, side effects, and clinical evaluations of Alirocumab.

## 2. Discussion

### PCSK9 Structure and Function

The 22-kb human PCSK9 gene, located on chromosome 1p32, contains 12 exons and 11 introns and codes for a 692 amino acid proteinase K-like serine protease. PCSK9 especially presents in the liver, but less amount is also found in the intestine, kidneys, and central nervous system. PCSK9 plays an important role in the metabolism of LDL-C as shown in Figure 1. LDL-C is bound to Low Density Level Receptor (LDL-R) and entered into hepatocytes through clathrin-plated vesicles. Recycling vesicles return LDL-R to the cell surface, whereas endosomes containing the LDL-C particles fuse with lysosomes, resulting in degradation of LDL-C, hydrolysis of cholesterol esters, and distribution of free cholesterol to the rest of the cell. At the hepatocyte plasma membrane, the catalytic domain of secreted PCSK9 associates with the LDL-R and entering the endosomal pathway. The low pH of endosomes increases the PCSK9 affinity for LDL-R, preventing the receptors from being recycled to the cell surface. Instead, the complex of PCSK9 and LDL-R is directed to a lysosome, where both components are degraded. [7,8]

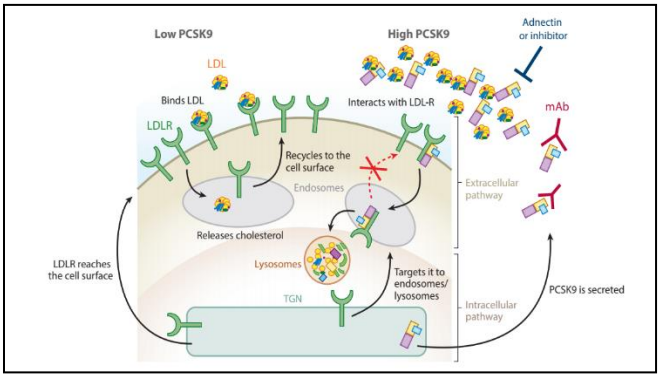


Figure 1. The role of PCSK9 in the metabolism of LDL receptors (LDL-R). The role of PCSK9 in LDL-R metabolism. When PCSK9 levels are high, the degradation of the LDL-R through extracellular and intracellular pathways is enhanced, resulting in increased degradation of the PCSK9–LDL-R complex in lysosomes. Low surface LDL-R levels lead to greater levels of circulating LDL-C. Conversely, if PCSK9 levels are low, then cell surface LDL-R levels are high, and LDL-R can be recycled to the cell surface after delivery of LDL-C particles to endosomes, resulting in lower circulating LDL-C levels. PCSK9 activity via the extracellular pathway can be inhibited by monoclonal antibodies (mAb) or adnectins. [9]

### Mechanism Of Action Alirocumab

Alirocumab is the PCSK9 inhibitor drug that was first approved by the FDA in the year 2015. Alirocumab is a human monoclonal antibody that has a high specificity and affinity to PCSK9. PCSK9 binds to LDL-R on the surface of hepatocyte to increase LDL-R degradation in liver. LDL-R is the main receptor which clears circulate LDL, therefore decreased level of LDL-R by PCSK9 results in higher LDL-C level in the blood. By inhibiting PCSK9 and LDL-R bond, alirocumab increases the amount of LDL-R available to clear LDL, thereby lowering LDL-C level [8,9]

### Dosing and Administration

The recommended initial dose of alirocumab is 75 mg subcutaneously administered once every 2 weeks. If the LDL-C response is not adequate, a dose of alirocumab can

be raised up to 150 mg subcutaneously every 2 weeks, which is the maximum recommended dose. In 4 to 8 weeks after the administration of the first dose of alirocumab, LDL-C levels should be tested to determine the response and the need for an additional dose adjustment. alirocumab is provided in two single-dose forms, including a prefilled pen or an autoinjector and a prefilled syringe. Each form delivers 1 mL of solution in either 75 mg/mL or 150 mg/mL. Alirocumab should be stored at 2 - 8° C in the box protected from light and it can be allowed at room temperature for 30 to 40 minutes before use.[10]

**Pharmacokinetics**

After administration of alirocumab at the dose of 75 mg to 300 mg subcutaneously, alirocumab is absorbed into the blood stream and the maximum concentration is reached at the average of 3-7 days. The bioavailability of alirocumab after subcutaneous injection is around 85%. Steady state concentration is reached after 3 to 4 administration. Alirocumab has a small volume of distribution of 0.04 - 0.05 L/kg after IV administration at a dose level of 3 to 12 mg/kg. Half life of single dose alirocumab is 5-8 days. In the multiple dose studies a Mean Residence Time (MRT) is about 17-20 day for alirocumab monotherapy. Statin therapy can increase PCSK9 production. Simultaneous administration of alirocumab with statins is estimated to shorten the half-life of alirocumab; Therefore the half-life of alirocumab is reduced down to 12 days. However, the distinction its half life is not considered clinically significant and do not need dose adjustment . [11,12]

Specific metabolism studies were not conducted because alirocumab is a protein. It is generally recognized that antibodies are metabolized by degradation into small peptides and individual amino acids. Alirocumab does not show any evidence in affecting CYP450 enzymes or protein transporter in co-administration with Statins. In low concentration , the elimination of alirocumab is dominated through the saturated bonds to its target (PCSK9), while at higher concentration of alirocumab is eliminated mostly through proteolytic pathway that is not saturated.[12]

**Safety**

Safety of alirocumab was evaluated at 2400 patients in the nine placebo controlled clinical trials. The median duration of treatment with alirocumab was 65 weeks. the mean of patient age is 59 years old and 60% of the total samples included were male. At the baseline, 37% of patients had a diagnosis of heterozygous familial hypercholesterolemia, and 66% had clinical CVD atherosclerosis. Side effects were reported in ± 2% of patients receiving alirocumab and considered more often than in those who received placebo. the side effects reported included nasopharyngitis (11.3%), site of injection reaction (7.2%), influenza (5.7%), urinary tract infection (4.8%), diarrhea (4.7%), bronchitis (4.3%), myalgia (4.2%), muscle cramps (3.1%), sinusitis (3.0%), cough (2.5%), bruises (2.1%), and musculoskeletal pain (2.1%). Side effects led to discontinuation of treatment at 5.3% of patients receiving alirocumab. The most common adverse reactions that caused the termination of the alirocumab were allergic reaction (0.6%) and increase in liver enzymes (0.3%).[10,17] Allergic observed in the alirocumab group may be related to alirocumab treatment, because allergic reactions have been associated with the use of other monoclonal antibodies. Alirocumab had no untoward effect with respect to the development or exacerbation of diabetes or increase of aminotransferase or creatine kinase level. [16]

**Clinical Outcomes**

The relevance of PCSK9 with coronary heart disease was determined from a human genetic study that identified increase mutation in PCSK9 functional genes associated with LDL-C level and premature coronary heart disease. On the contrary, the PCSK9 mutation is associated with lower serum LDL-C level , exposure to a less LDL-vascular structure and reduction in the risk of coronary heart disease. In addition, healthy subjects with loss function of PCSK9 seemed to have a serum concentration of LDL-C as low as 14 mg/dL without adverse health effects.[13]

Long-term research on the double-blind ODYSSEY study was conducted to gather long-term data on the safety and efficacy of alirocumab in reducing LDL cholesterol levels. This trial enrolled 2,341 patients at high risk for Cardiovascular events with LDL-C levels of at least 70 mg/dl while receiving treatment with statins at the maximum tolerated dose, with or without other lipid-lowering therapy. Subjects randomly received alirocumab or placebo which were administered subcutaneously every two weeks for 78 weeks. In the 24$^{th}$ week, the percentage of average change in LDL cholesterol level from the beginning was 61% in alirocumab group compared to 0.8% in placebo group; the effect of this treatment persisted during the treatment period of 78 weeks. Over the course of the trial, alirocumab significantly reduced the risk of the primary end point by 15% compared to placebo (HR[*] 0.85, 95% CI[†] 0.78–0.93, $P$ = 0.003). The effects of alirocumab on the individual components of the composite end points, including coronary heart death, were directionally

[*] HR, Hazard Ratio
[†] CI, Confidence Interval

consistent. A nominal of 15% reduction (HR 0.85, 95% CI 0.73–0.98) in all-cause mortality with alirocumab treatment compared to placebo was also reported, which was not statistically significant given to two nonsignificant outcomes (CHD death and cardiovascular death) in the testing hierarchy. The side effects were similar in both groups, but patients who received alirocumab experienced more reactions at the injection site, myalgia, and neurocognitive events. Post hoc security analysis revealed that major adverse heart events were significantly lower with alirocumab treatment compared to placebo (1.7% vs 3.3%, HR 0.52, 95% CI 0.31-0,90, P = 0.020).[14,15]

In another trial, 2341 high-risk patients were randomly assigned to either the PCSK9 inhibitor alirocumab or placebo. As compared to placebo, alirocumab reduced LDL cholesterol levels by 62 percentage points at 24 weeks, with a consistent reduction over a period of 78 weeks of treatment.[16]

**Special Population**

Pregnancy.

Alirocumab should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus. There is no increase in the frequency of malformations or other direct or indirect adverse effects on the fetus with a mother using Alirocumab. Animal studies showed no evidence of increase occurrence of fetal damage. [10,18]

Children.

The safety and effectiveness of alirocumab in child patients has not been established.[10]

Elderly.

In clinical studies, efficacy and tolerability of alirocumab in older patients (age ≥ 65 years) is similar to younger patients.[10]

Renal impairment.

There is no necessary dose adjustment of alirocumab for patients with impaired mild or moderate renal function, no data is available regarding patients with severe renal impairment. [19,20]

Hepatic impairment.

No dose adjustment of alirocumab is required for patients with mild or moderate hepatic impairment; There is no data available about patients with severe hepatic impairment.[10,20]

**Conclusion**

Alirocumab is a PCSK9 inhibitor with minimal side effects that is safe and effective in the application of patients who require additional reduction in LDL-C levels. By inhibiting PCSK9 action in the liver, this drug can reduce circulating LDL-C in CVD patients who cannot be controlled with a maximum dose of statin. Compared to placebo, alirocumab reduced LDL cholesterol levels by 62 percentage points at 24 weeks, with a consistent reduction over 78 weeks of treatment.

**3. Reference**


1. Benjamin E, Virani S, Callaway C, Chamberlain A, Chang A, Cheng S, et al. Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. Circulation. 2018; 137(12).
2. Sirimarco G, Labreuche J, Bruckert E, Goldstein L, Fox K, Rothwell P et al. Atherogenic Dyslipidemia and Residual Cardiovascular Risk in Statin-Treated Patients. Stroke. 2014;45(5):1429-1436.
3. Karalis D, Victor B, Ahedor L, Liu L. Use of Lipid-Lowering Medications and the Likelihood of Achieving Optimal LDL-Cholesterol Goals in Coronary Artery Disease Patients. Cholesterol. 2012;2012:1-7.
4. Collins R, Reith C, Emberson J. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016; 388:2532–2561
5. US Food and Drug Administration, Office of Medical Products and Tobacco, Center for Drug Evaluation and Research, Division of Metabolism and Endocrinology Products. Briefing information for the June 9, 2015, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC). BLA 125559, Praluent (alirocumab) injection. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm449863.htm. Updated June 5, 2015. Accessed May, 2019.
6. Roth M, McKenney M, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012; 367:1891-1900.
7. Bergeron N, Phan B, Ding Y. Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition: A New Therapeutic Mechanism For Reducing Cardiovascular Disease Risk. Circulation. 2015; 132:1648–1666.
8. Burke A, Dron J, Hegele R, Huff M. PCSK9: Regulation and Target For Drug Development For Dyslipidemia. Annu. Rev. Pharmacol. Toxicol. 2017; 57:223–244.

9. Seidah N, Zuhier A, Chetien M, Mbikay M. PCKS: a key modulator of cardiovascular health. Circ. Res. 2014; 114:1022–1036.
10. Praluent (alirocumab) injection [prescribing information]. Bridgewater, NJ: sanofi-aventis US; Tarrytown, NY: Regeneron Pharmaceuticals; October 2015.
11. Nicolas X, Djebli N, Rauch C, Brunet A, Hurbin F, Martinez J et al. Population Pharmacokinetic/ Pharmacodynamic Analysis of Alirocumab in Healthy Volunteers or Hypercholesterolemic Subjects Using an Indirect Response Model to Predict Low-Density Lipoprotein Cholesterol Lowering: Support for a Biologics License Application Submission: Part II. Clinical Pharmacokinetics. 2018;58(1):115-130.
12. Lunven C, Paehler T, Poitiers F, Brunet A, Rey J, Hanotin C et al. A Randomized Study of the Relative Pharmacokinetics, Pharmacodynamics, and Safety of Alirocumab, a Fully Human Monoclonal Antibody to PCSK9, After Single Subcutaneous Administration at Three Different Injection Sites in Healthy Subjects. Cardiovascular Therapeutics. 2014;32(6):297-301.
13. Roth M, Goldberg C, Catapano L. Antidrug Antibodies in Patients Treated with Alirocumab. N Engl J Med. 2017;376(1): 589-590
14. Schwartz G, Bessac L, Berdan L, Bhatt D, Bittner V, Diaz R et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial. American Heart Journal. 2014;168(5):682-689.
15. Schwartz G, Bessac L, Berdan L, Bhatt D. The ODYSSEY OUTCOMES trial: topline results — alirocumab in patients after acute coronary syndrome. Presented at the 67th Scientific Sessions of the American College of Cardiology (2018)
16. Robinson G, Farnier M, Krempf M. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N. Engl. J. Med. 2015; 372(1): 489–99.
17. Ginsberg N, Rader J, Raal J. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. Cardiovasc. Drugs Ther. 2016;30:473–83.
18. Achimastos A, Alexandrides T, Alexopoulos D, Athyros V, Bargiota A, Bilianou E. Expert consensus on the rational clinical use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Hormones (Athens). 2016;15:8–14.
19. Toth P, Dwyer J, Cannon C, Colhoun H, Rader D, Upadhyay A et al. Efficacy and safety of lipid lowering by alirocumab in chronic kidney disease. Kidney International. 2018;93(6):1397-1408.
20. Handelsman Y, Lepor N. PCSK9 Inhibitors in Lipid Management of Patients With Diabetes Mellitus and High Cardiovascular Risk: A Review. Journal of the American Heart Association. 2018;7(13).