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Therapeutic effects of Alirocumab on atherosclerosis: mechanisms and clinical applications

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Abstract. Lower low-density lipoprotein cholesterol (LDL-C) is one of the most critical steps to alleviate atherosclerosis. LDL-C accumulation in the intima of arteries leads to oxidized LDL and the formation of foam cells, followed by a core area of atherosclerotic plaques. Proprotein convertase subtilisin/keeping type 9 (PCSK9) can increase the concentration of LDL-C levels by lowering the density of LDL receptors. Alirocumab, as a monoclonal antibody, is a PCSK9 inhibitor that decreases LDL-C levels and reduces the prevalence of cardiovascular disease. However, the immune response issues and mechanism of action of Alirocumab, as well as the safety and efficacy of Alirocumab, remain to be elucidated. This review explains the mechanism of action and process of atherosclerosis, together with the present applications of Alirocumab as PCSK9 in atherosclerosis. PCSK9 inhibitors reduce the density of LDL receptors and treat the effects of various diseases on atherosclerosis. Furthermore, Alirocumab has shown a decrease in protein cholesterol levels or percentage of atherosclerotic volume through multiple clinical trials, including ODYSSEY, PACMAN-AMI, and ARCHITECT. Further mechanistic research and clinical trials are required to approve the therapeutic role and promote clinical applications of Alirocumab.

Keywords: Alirocumab, Atherosclerosis, PCSK9 inhibitor.

1. Introduction

Atherosclerosis is a chronic inflammatory disease that occurs in the blood vessels of the arteries. The thickening and stiffness of the blood vessels that transport oxygen and nutrients to other parts of the body is what causes atherosclerosis, the flow of blood to organs and tissues can be hindered by it at times. As societies continue to age, the prevalence of atherosclerosis is on the rise [1]. Atherosclerosis is no longer restricted to Western countries but is strongly associated with the majority of deaths worldwide. In particular, the proportion of middle-aged men and women with subclinical atherosclerosis is 71% and 43%, respectively. According to statistics, cardiovascular diseases were responsible for 32% of all global deaths in 2019, with a total of 17.9 million deaths. Atherosclerosis, of which cardiovascular disease is one of the major components, becomes the cause of most of the death cases, 85% of which come from heart attacks or strokes. To slow the progression of atherosclerotic plaques, the main objective of the therapeutic approach is to decrease low-density lipoprotein cholesterol (LDL-C) levels, and there is no doubt that lipid-lowering therapy has relied on statins as its foundation for many years [2].

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Alirocumab is a Pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, and it has been found to have a therapeutic effect on atherosclerosis. Alirocumab is used in the treatment of hyperlipidemia to achieve a reduction in cholesterol levels and the prevalence of cardiovascular disease. To verify its safety and efficacy, the study enrolled 18,924 patients at 1,315 study centers who were diagnosed with acute coronary syndrome (ACS) within 12 months prior to study inclusion. After 2.8 years of follow-up, Alirocumab was found to have a 54.7% lower LDL-c level in patients treated with placebo in the study, while the incidence of the primary outcomes of nonfatal myocardial infarction, The alecuminumab group had a lower rate of nonfatal ischemic stroke and unstable angina requiring hospitalization (9.5%) than the placebo group (11.1%) [3]. The results showed that intervention with a monoclonal antibody against PCSK9 can lower the probability of atherosclerotic cardiovascular disease while significantly reducing LDL-C levels. In addition, numerous pharmacologic and clinical studies have been conducted in addition to the basic understanding of atherosclerosis and Alirocumab [3].

This article focuses on studies involving Alirocumab as a PCSK9 enzyme inhibitor in the treatment of atherosclerosis, where the efficacy of Alirocumab has been validated. Therapeutic antibodies are molecular reagents that bind stably to identify proteins that exhibit high specificity and affinity. In spite of certain drawbacks, including unclear mechanisms of action, low diffusion efficiency within tissues, and impaired immune response, successful clinical translation of antibody drugs is now possible due to recent advances in antibody engineering technology.

2. PCSK9 in atherosclerosis

2.1. Mechanisms of atherosclerosis

Atherosclerosis occurs when fats, cholesterol, and other substances collect in and on the walls of the arteries, which is called plaque. Plaque narrows the arteries and impedes blood flow. In addition, plaque can rupture and form blood clots. Atherosclerosis is considered to be the result of elevated cholesterol [3]. The complexity involved in the disease and the participation of several risk elements remain to be further investigated, but it is widely recognized that increased cholesterol levels herald the first signs of atherosclerosis. Lower concentrations of LDL-C than physiologically necessary cause LDL to accumulate in the intima of the arteries, leading to atherosclerosis. Lipids in the intima are converted to oxidized LDL by oxidative modification and are taken up by monocyte-derived macrophages to form foam cells. These foam cells accumulate within the intima and are inhibited from migration, which in turn forms the center of lipid-rich atherosclerotic plaques by binding to cholesterol and apoptotic necrotic cells [3].

Sudden numbness or weakness in the arms or legs, difficulty speaking or slurred speech, temporary blindness in one eye, and drooping of the facial muscles can be caused by atherosclerosis. These may be signs of a transient ischemic attack. Without in-time examination, a transient ischemic attack can lead to a stroke. If atherosclerosis of the arteries affects the heart, chest pain or angina may occur. Symptoms of peripheral artery disease, such as a drop in blood pressure in the extremities or sudden pain when walking may occur when atherosclerosis affects arteries in arms or legs. If atherosclerosis affects the kidney, patients may be at risk for high blood pressure or kidney failure [4].

2.2. PCSK9 in atherosclerosis

PCSK9 inhibitors are a new class of lipid-lowering drugs, proteins that increase the value of LDL-C by decreasing the density of LDL receptors (LDLR) on the surface of liver cells. Globally, effective treatment with PCSK9 inhibitors, including monoclonal antibodies that block their circulating activity, has reduced the incidence of atherosclerosis by at least 20%. PCSK9's ability to target LDLR degradation is utilized by pathogens like dengue virus to improve their ability to infect cells. Thus, these new targets shed light on the relationship between atherosclerosis, viral infections, cancer metastasis, and PCSK9. PSSK9 inhibitors hold the promise of becoming a modern weapon in the treatment of diseases other than hypercholesterolemia and their effects on atherosclerosis. In patients with acute coronary syndromes, LDL-C concentrations can be reduced by up to 60%, accompanied by concomitant

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decrease in the probability of main adverse cardiovascular incidents. Combination therapy with statins and PCSK9 monoclonal antibodies resulted in positive changes in coronary atherosclerosis after myocardial infarction, consistent with a trend toward plaque loading [5]. The PCK9 protein is involved in the pathophysiology of atherosclerosis not only by acting on the LDLR, but also by affecting endothelial cells, smooth muscle cells, activation of inflammatory pathways and platelet function.

2.3. Alirocumab as a PCSK9 inhibitor

Alirocumab is a monoclonal antibody known as a PCSK9 inhibitor, which is specifically designed to inhibit the preprotein convertase Bacillus subtilis proteobacterial protease type 9 (known as PCSK9). The effectiveness of alirocumab in lowering LDL cholesterol levels in patients treated with statins has been demonstrated. Alirocumab can be used alone or in combination with other cholesterol-lowering medications [5]. Since PCSK9 is a down-regulator of the LDLR, Alirocumab works by inhibiting the action of PCSK9, thereby increasing the uptake of LDL-C by the liver and thus lowering LDL-C levels in the blood (Figure 1) [5]. In addition, the Alirocumab is effective in reducing the risk of heart attack, stroke, and the need for hospitalization for certain types of chest pain (unstable angina). However, Alirocumab also has side effects such as rash, itching or hives, and swelling of the face, lips, or tongue [5].

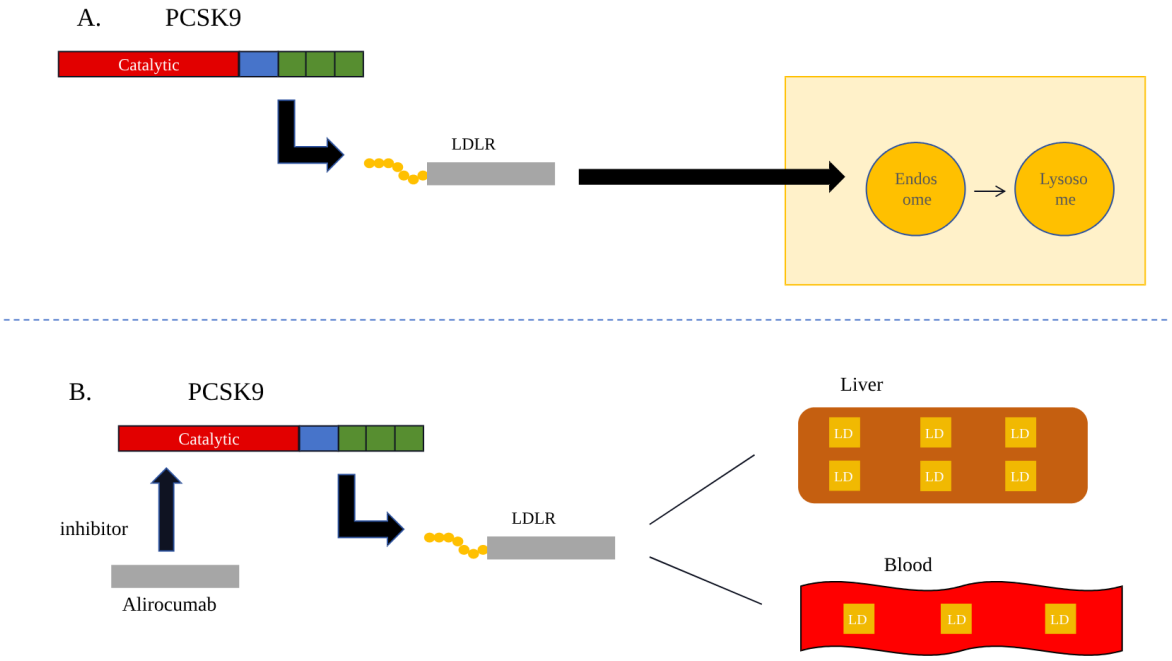

Figure 1. Schematic representation of LDLR degradation to lysosomes by induction of PCSK9 and the mechanism of alriocumab. A) the catalyst in PCSK9 can help degrade LDLR into the cell. B) the fact that the inhibition of PCSK9 by Alirocumab resulted in an increase in the amount of lipid droplets (Abbreviations: LD) in the liver and a decrease in the blood level of LD. Figure credit: original.

3. Clinical trials

There have been clinical trials of therapeutic efficacy of Alirocumab monoclonal antibody in atherosclerosis, including ODYSSEY, PACMAN-AMI study and ARCHITECT (Table 1).

3.1. ODYSSEY

An international, randomly allocated, double-blind, placebo-controlled, parallel-group investigation, the ODYSSEY LONG TERM experiment is divided into three stages and has over 300 locations spread across 27 countries in Africa, Europe, North America, and South America. The trial was conducted in

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adult patients who met the criteria for heterozygous familial hypercholesterolemia (determined on the basis of genotype or clinical diagnosis), or who either had an atherosclerosis or were at danger of getting one. An LDL cholesterol concentration of 70 mg/dL (1.8 mmol/L) or more at testing was one of the enrollment requirements. After a 3-week screening period, patients who were enrolled were randomly divided into two groups and assigned to receive either Alirocumab (150 mg) or placebo each week for a total of 78 weeks, The administration of both regimens is done through a single 1-ml subcutaneous injection. The study involved 2341 patients who were instructed to adopt a stable therapeutic lifestyle change diet, 1553 in the Alirocumab group and 788 in the placebo group. All research subjects were 60 years old and 37.8% were female. The 2,338 patients who were analyzed for safety, with 1,550 in the Alirocumab group and 788 in the placebo group, had an average drug exposure time of 70 weeks, and a total of 2,061 patients received Alirocumab in the study Take 150 mg every two weeks. Results from the ODYSSEY LONG TERM trial showed that Alirocumab had a 62 percentage point reduction in LDL cholesterol levels compared to placebo after 24 weeks of treatment and sustained the reduction over the 78-week treatment period. Following this trial, there is evidence that Alirocumab reduces cardiovascular events [6].

3.2. PACMAN-AMI

The PACMAN-AMI study used serial multimodal intracoronary imaging to study the effect of Alirocumab on coronary atherosclerosis in patients with acute myocardial infarction. The four-year trial was double-blind, placebo-controlled, and randomized, with a total of 300 European patients undergoing interventional percutaneous coronary artery therapy at nine academic hospitals. Subjects were randomly assigned to receive subcutaneous injections of 150 mg of Alirocumab or placebo at two-week intervals, followed by treatment lasting 52 weeks and concomitant high-intensity statin therapy (20 mg of rosuvastatin) starting less than one day after the emergency percutaneous coronary intervention was performed. At 52 weeks, 300 randomly selected patients treated with Alirocumab showed a mean decrease in percent atherosclerosis volume of 2.13% compared with -0.92% in the placebo group. In 70.7% of patients who received Alirocumab, adverse events occurred, compared to 72.8% of patients who received placebo. Therefore, further studies are necessary to determine whether Alirocumab improves clinical outcomes in this patient population [7].

3.3. ARCHITECT

ARCHITECT is an open-label, multicenter, single-arm clinical trial designed to evaluate the effect of Alirocumab on the structural composition of coronary atherosclerotic plaque volume, specifically characterizing subjects with familial hypercholesterolemia in the absence of clinically atherosclerotic cardiovascular disease over a 78-week course. 104 subjects underwent coronary artery computed tomography angiography, and final examinations were completed at 78 weeks. While receiving high-dose statin therapy, every 14 days, Alirocumab was administered subcutaneously to each patient in a dose of 150 mg. The research included 104 patients with a mean age of 53.3 years. Coronary artery lesion rates trended downward during follow-up, with a significant decrease in the proportion of unstable cores (composed of fibrofatty and necrotic plaques). Further studies in patients with familial hypercholesterolemia and patients with larger unstable cores are needed to validate the improved efficacy of therapy with Alirocumab in patients with higher baseline PB, especially in the setting of high-intensity statin therapy [8].

3.4. Other clinical trials

Clinical trials revealed that Alirocumab has a very low rate of immunogenicity. An analysis conducted 10 studies in 4747 patients to evaluate the impact of Alirocumab antidrug antibodies on the safety and efficacy of LDL cholesterol reduction. The results showed that of the 3039 patients in the Alirocumab group, only 155 (5.1%) developed anti-drug antibodies. Of the 1,708 patients in the placebo group, 17 (1.0%) were found to have developed anti-drug antibodies; whereas, of the 44 patients treated with Alirocumab, 3 (0.2%) were observed to have sustained the development of anti-drug antibodies. Thus,

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antibodies were produced in only a very small number of patients treated with Alirocumab, while LDL-C continued to decline in this group of patients [2].

Table 1. Therapeutic efficacy of Alirocumab monoclonal antibody in atherosclerosis

Studies	Design	Treatment Cycle	Effects	References
ODYSSEY	Randomized, double-blind, placebo-controlled, parallel-group	78 weeks	Significant reduction in LDL cholesterol levels	[6]
PACMAN-AMI	Double-blind, placebo-controlled, and randomized	52 weeks	The percentage of volume of arterial coronary sclerosis decreased more and the probability of adverse events was relatively small.	[7]
ARCHITE-CT	An open-label, multicenter, single-arm clinical trial	78 weeks	There is a downward trend in the proportion of both arterial coronary lesions and unstable cores.	[8]
Others	None	None	Antibody production accompanied by sustained LDL-C decline in patients treated with alriocumab.	[2]

4. Conclusion

The intervention of PCSK9 by Alirocumab reduces both LDL-C levels and the probability of atherosclerosis occurring. When LDL accumulates in the intima of arteries, lipids are oxidized and converted to oxidized LDL, followed by foam cells formed, leading to the formation of the core area of atherosclerotic plaques by combining with other necrotic cells. PCSK9 protein reduces the density of LDL receptors, followed by increasing the concentration of LDL-C levels. Alirocumab, as an inhibitor of PCSK9, can reduce LDL-CR's ability to decline the risk of heart disease and chest pain. However, the therapeutic effect of this class of monoclonal antibodies on other diseases has not been studied with enough evidence. Significant reductions in LDL cholesterol levels in patients with the application of Alirocumab have been found in clinical trials, with a smaller probability of adverse events and an important decrease in the proportion of unstable cores in comparison with placebo-treated patients. Further validation of the improved efficacy of treatment with Alirocumab in patients with familial hypercholesterolemia in the setting of high-intensity statin therapy is needed for patients with a high baseline PB.

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