Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/59/20241370

PCSK9 inhibitors in the research progress of atherosclerotic cardiovascular diseases

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Abstract. Atherosclerosis is a major global health issue, with cardiovascular diseases leading to over 4 million deaths in China in 2019. Effective management of atherosclerosis is crucial for reducing its incidence and mortality, with LDL-C reduction being a key strategy. This study examines the role of PCSK9 in atherosclerosis and the therapeutic potential of PCSK9 inhibitors, focusing on their ability to lower LDL-C levels and prevent cardiovascular events A literature review was conducted, analyzing the mechanisms of PCSK9 in lipid metabolism and the efficacy of various PCSK9 inhibitors, including monoclonal antibodies, antisense oligonucleotides, and small interfering RNA. PCSK9 inhibitors, such as Alirocumab, evolocumab, and Inlisiran, have demonstrated effectiveness in reducing LDL-C levels. Inlisiran, in particular, offers a long-lasting effect and has shown significant potential in clinical trials. Nucleic acid-based treatments are emerging as promising options with advantages such as sustained efficacy and a broad application scope, despite the need for further research to address delivery and off-target effects.

Keywords: PCSK9, Atherosclerotic, Cardiovascular disease, PCSK9 inhibitors, LDLC, LDLR.

1. Introduction

Atherosclerosis poses a significant risk to global health, with cardiovascular diseases accounting for over 4 million deaths in China in 2019, the highest globally [1]. The formation and rupture of atherosclerotic plaques, leading to thrombosis, are pivotal in the pathogenesis of these diseases. Effective management of atherosclerosis is essential for lowering their incidence and mortality rates [2]. Atherosclerosis is influenced by a variety of factors, including lipids and inflammatory mediators [3]. The connection between cholesterol and heart disease was first established by Nikolai Anitschkow in 1913, who observed that a diet rich in cholesterol in rabbits increased atherosclerotic progression[4].

LDL-C is identified as a primary contributor to atherosclerosis, with endothelial dysfunction facilitating its infiltration into the arterial intima, resulting in foam cell and fibrous cap development, and plaque formation[5]. The precise immunological mechanisms of atherosclerosis remain to be fully elucidated. Nonetheless, it is established that lowering LDL-C levels can mitigate atherosclerotic risk.

Statins are the primary pharmacological agents for treating atherosclerosis, complemented by other classes such as fibrates and ezetimibe [6-8]. Despite their efficacy, statins are associated with muscle-related side effects and issues of drug tolerance. PCSK9 inhibitors offer a promising alternative, addressing the limitations of statin therapy. Evidence suggests that the addition of PCSK9 inhibitors to

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intensive statin regimens can further decrease LDL-C levels and reduce cardiovascular events, with a safety profile similar to that of control treatments [9].

This review will delve into the role of PCSK9, the pathological underpinnings of atherosclerotic cardiovascular diseases, and the therapeutic potential of PCSK9 inhibitors in managing these conditions.

2. Atherosclerosis: Pathophysiological Mechanisms

Atherosclerosis initiates its development at an early stage, potentially during childhood, and is a chronic inflammatory process instigated by cholesterol. A plethora of evidence from epidemiological, genetic, and clinical intervention studies underscores the pivotal role of low-density lipoprotein cholesterol (LDL-C) in the genesis of atherosclerotic plaques in the coronary arteries. The mechanisms through which LDL-C contributes to plaque formation include: (1) the engulfment of LDL-C particles by foam cells[10]; (2) the release of inflammatory lipids with biological activity upon LDL-C oxidation, which can have both localized and systemic impacts[11]; (3) the formation of extracellular lipid deposits, particularly cholesterol crystals, as LDL-C particles undergo alteration; (4) the provocation of innate immune responses that facilitate the attraction of various immune-inflammatory cells, such as monocytes/macrophages, neutrophils, lymphocytes, and dendritic cells, leading to chronic inflammation that can result in cell death through apoptosis or necrosis, thus fostering the development of a necrotic core[12-14]; (5) the activation of antigen-specific T cell reactions and the induction of adaptive immune responses through modifications of apolipoprotein B100 (ApoB100) or its breakdown. Considering the factors that lead to LDL-C infiltration and retention in the arterial intima, along with the ensuing immune-inflammatory reactions in the arterial wall, the medical community generally agrees that significantly reducing LDL-C levels is a key determinant in the reversal of coronary atherosclerotic plaques [15].

3. The Mechanism of PCSK9 in Lipid Metabolism

PCSK9, belonging to the proprotein convertase family, is primarily produced by the liver and also found in various other tissues[16]. Initially formed as an inactive precursor in the liver's endoplasmic reticulum, it undergoes activation before entering the bloodstream. Once in plasma, PCSK9 interacts specifically with the epidermal growth factor-like domain A (EGF-A) on hepatic Low-Density Lipoprotein Receptor (LDLR), hindering their ability to engage with LDL cholesterol. Normally, LDL receptors facilitate the uptake and subsequent breakdown of LDL cholesterol, with the receptors being reused for further cholesterol clearance. However, the interaction of PCSK9 with these receptors and cholesterol forms an internalizable complex that is degraded, thus diminishing the availability of LDL receptors for recycling. This results in a reduced capacity for cholesterol clearance and an increase in circulating LDL cholesterol levels. On the flip side, diminished PCSK9 levels enhance LDL receptor availability, promoting a decrease in serum LDL cholesterol [17-18].

4. The Role of PCSK9 Inhibitors in Lowering LDLC

4.1. PCSK9 Antibodies

Alirocumab (marketed as Praluent) and evolocumab (Repatha) are recognized as the prominent monoclonal antibodies that target PCSK9, with regulatory clearance in both the U.S. and the EU[19]. The FOURIER study aimed to substantiate the clinical benefits of evolocumab in high-risk individuals. It included participants who had previously experienced a heart attack, stroke without bleeding, or had symptoms of peripheral artery disease, totaling 27,564. These subjects continued on their statin regimens while receiving either evolocumab or a placebo. Over 2.2 years, the study monitored the occurrence of cardiovascular issues, with the evaluation of primary and secondary endpoints linked to the decline in LDL levels. At the 48-week mark, there was a significant 59% decrease in LDL-C levels in the group administered evolocumab when juxtaposed with the placebo group. Additionally, the rate of major adverse cardiovascular events was comparatively lower in the evolocumab recipients at 9.8%, contrasting with the 11.3% rate observed in the placebo group [19-22].

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4.2. PCSK9 ASO

Key drugs within the antisense oligonucleotide category are ISIS 394814, SPC5001, and SPC4061. Experimental protocols have administered the artificial ISIS 394814 to C57BL/6 mice characterized by hyperlipidemia, with bi-weekly injections sustained over six weeks. Outcomes from these experiments have demonstrated that the application of ISIS 394814 effectively reduced the expression of PCSK9 mRNA in the liver, leading to an enhancement in LDLR expression within hepatocytes by twofold. Furthermore, it induced a significant decrease in both total plasma cholesterol and LDL-C levels, by 53% and 38% respectively [23]. In parallel, SPC5001 and SPC4061, when subjected to trials on primates, have each proven capable of achieving over a 50% reduction in LDL-C levels[24]. Nonetheless, the initial clinical trials for SPC5001 and SPC4061, encompassing both healthy volunteers and individuals with familial hypercholesterolemia, were halted ahead of schedule. SPC5001 was linked to minor to moderate local reactions at the injection site along with signs of renal tubular toxicity[25]. The specific cause for the termination of the SPC4061 study has not been disclosed. These incidents underscore the necessity for continued research into the safety profile of PCSK9 inhibitory agents.

4.3. PCSK9 siRNA

The mechanism by which siRNAs specific to PCSK9 operate is by inhibiting the translation process of PCSK9[26]. Inlisiran stands as the sole siRNA of its kind for PCSK9, being a synthetically crafted siRNA that attaches to GalNAc, which leads to a prolonged and precise suppression of RNA associated with PCSK9 production. This results in a decrease in PCSK9 levels both within cells and in the bloodstream[27].

Early-stage clinical trials have evaluated the effectiveness of Inlisiran, both in a single administration across various dosages and in a multi-dose format. The single-dose approach showed a decrease in LDL-C levels ranging from 36% to 50%, contingent upon the dosage used. The multi-dose strategy demonstrated an even more pronounced reduction, with LDL-C levels dropping between 45% to 59%[28]. PCSK9 levels experienced an 83% reduction. In contrast to monoclonal antibodies, Inlisiran offers an extended period of efficacy, with effects persisting for a minimum of 180 days post-treatment initiation[28]. This suggests that Inlisiran could substantially decrease LDL levels when administered every three to six months[28]. Further studies, including a Phase 2 trial and a meta-analysis with a substantial patient cohort, corroborated these findings, indicating significant LDL-C reductions with Inlisiran treatment[29-30]. In a specific study involving heterozygous familial hypercholesterolemia patients (Orion-9) [31], Inlisiran was found to notably lower LDL-C levels by 39.7%, contrasting with an increase observed in the placebo group, highlighting a significant therapeutic advantage (95% CI, −53.5 to −42.3; $P<0.001$).

5. Conclusion

Heart-related illnesses are the primary cause of fatalities in our nation, making their management a key strategy for lowering death rates. Therapies for cardiovascular conditions currently encompass statins, ezetimibe, and inhibitors of the PCSK9 enzyme. Despite their benefits, statins are not without drawbacks, such as muscle-related issues and potential liver harm, prompting interest in nucleic acid-based pharmaceuticals and the identification of novel treatment targets.

Nucleic acid-based medications offer several benefits, including a reduced likelihood of resistance, a wider range of applications, and enduring efficacy. They have the potential to address health conditions at a fundamental level. Non-coding RNAs, which encompass small interfering RNA (siRNA), long non-coding RNA (lncRNA), and microRNA (miRNA), have been identified as having significant biological functions. MiRNAs are known to regulate gene expression by engaging with the 3' untranslated regions of their target mRNAs, which can halt the synthesis of proteins or lead to their breakdown. While challenges remain, such as ensuring targeted delivery beyond the liver and mitigating off-target effects, advancements in technology could pave the way for swift progress in this domain.

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