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| RESEARCH ARTICLE

Research Progress on Multiple Effects and Clinical Application of Proprotein Convertase Subtilisin-kexin9 Inhibitors

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| ABSTRACT

PCSK9 inhibitors (Proprotein convertase subtilisin-kexin9 inhibitors) not only have a good lipid-lowering effect but also have the effects of improving cardiovascular outcome, anti-inflammation, reducing oxidative stress and improving vascular endothelium. In recent years, the continuous research and development of PCSK9 inhibitors have provided new ideas for the treatment of cardiovascular diseases. This article reviews the multiple action mechanisms of PCSK9 inhibitors and their research in kidney disease and cerebrovascular diseases.

| KEYWORDS

Proprotein convertase subtilisin-kexin9 inhibitor; Vascular endothelium; Pleiotropy; Blood lipids; Cardiovascular outcomes; Inflammation; Oxidative stress; Cerebrovascular disease; Kidney disease

| ARTICLE INFORMATION

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1. Introduction

PCSK9 is involved not only in lipid metabolism but also in the formation of atherosclerosis. As a new class of lipid-lowering drugs, PCSK9 inhibitors not only have lipid-lowering effects but also have pleiotropic effects, such as improving cardiovascular outcomes and improving vascular endothelial function. The continuous development and application of PCSK9 inhibitors in recent years has not only provided new ideas for the prevention and treatment of cardiovascular diseases but also provided new ideas for the treatment of diseases in other fields. This article reviews the research on the pleiotropic mechanism of PCSK9 inhibitors and their research on diseases in other fields, especially kidney disease and cerebrovascular disease.

2. Mechanism of PCSK9 inhibitors

At present, PCSK9 inhibitors, including evolocumab, alirocumab, and inclisiran, are widely used. In general, PCSK9 inhibitors can be roughly divided into four categories: monoclonal antibody inhibitors, nucleic acid drugs, small molecules and vaccine drugs. (1) Monoclonal antibody inhibitors, such as evolocumab and alirocumab. The monoclonal antibody of PCSK9 blocked the interaction between PCSK9 and LDL-R(Low-Density Lipoprotein Receptor) and effectively inhibited the degradation of LDL-R, thus reducing the level of LDL-C(Low-Density Lipoprotein Cholesterol). Similar peptides blocked the binding between the EGF-A domain of LDL-R and PCSK9, thus inhibiting PCSK9. (2) Nucleic acid drugs, such as ASOs (antisense oligonucleotides), siRNA and, CRISPR/Cas9, etc.ASOs bind to the mRNA of the target PCSK9 gene through Watson-Crick base pair interaction, which hinders the expression of the target gene.SiRNA can inhibit the degradation of mRNA in a specific sequence, thus hindering the expression of the PCSK9 gene and affecting the synthesis of protein (Ray, 2017). Inclisiran, as a representative drug of nucleic acid inhibitor, has been

applied in the clinic and has shown a positive effect in reducing blood lipids (Ray, 2020). CRISPR/Cas9 can effectively inhibit the expression of the PCSK9 target gene by inducing DNA double strand breaks in host cells, which can lead to mismatch, recombination and non-homologous end connection. (3) Small molecules, such as BMS-962476. Small molecular drugs can cause the allosterization of PCSK9 protein, which in turn affects the binding of PCSK9 and LDLR (Mitchell, 2014). (4) Vaccine drugs, such as L-IFPTA + vaccine, can inhibit circulating PCSK9 activity (Momtazi-Borojeni, 2021). Researchers constructed an IFPT(immunogenic peptide construct) fused with PCSK9-tetanus protein on the surface of LNP(liposomal nanoparticles) and then mixed it into an alum adjuvant (Momtazi-Borojeni, 2019). L-IFPTA+vaccine can induce PCSK9 antibody.PCSK9 antibody directly targets and eliminates circulating PCSK9 in blood.

3. Pleiotropic effects of PCSK9 inhibitors

3.1 Decrease blood lipids

LDL-C in plasma combines with LDL-R and enters cells. After fusion with lysosomes, it is hydrolyzed by lysosomal hydrolase.PCSK9 is a key protein in lipid metabolism. After PCSK9 binds to LDL-R, LDL-R is degraded, thus reducing the clearance of LDL-C (Momtazi-Borojeni, 2019). PCSK9 inhibitor inhibits the combination of PCSK9 molecule and LDL-R by binding with PCSK9 molecule, thus reducing the degradation of LDL-R, thus increasing the uptake of LDL-C in plasma by LDL-R, thus reducing the concentration of LDL-C. Early phase II clinical trials show that PCSK9 inhibitors can effectively reduce LDL-C (at least 40%) (Koren, 2012). For the extremely high-risk patients with atherosclerotic cardiovascular disease whose LDL-C is still not up to the standard after receiving the maximum tolerated dose of statins, after 12 weeks of treatment with PCSK9 inhibitors, more than 90% of the patients have achieved the established lipid-lowering goal (Desai, 2014). In addition, patients with hyperlipidemia who received PCSK9 inhibitors combined with statins experienced a significant (at least 40%) reduction in LDL-C from baseline after 3 months of PCSK9 inhibitor therapy (Giugliano, 2012). In the OSLER study, the reduction in LDL-C levels was maintained at approximately 50% in patients who continued PCSK9 inhibitor therapy, whereas in patients who did not continue treatment, LDL-C levels eventually returned to baseline (Koren, 2014). For the treatment group receiving PCSK9 inhibitors, other non-major intervention targets such as non-high density lipoprotein cholesterol, triglyceride and lipoprotein (a) levels decreased in varying degrees, but the content of high density lipoprotein cholesterol increased. OSLER-1 study found that PCSK9 inhibitors were long-lasting, effective, and well tolerated in patients with hyperlipidemia (Koren, 2019). In the phase III clinical study of PCSK9 inhibitors, the MENDEL-2 study found that PCSK9 inhibitor monotherapy for 12 weeks is safe and effective (Koren, 2014). The LAPLACE-2 study found that in terms of combination therapy, when baseline LDL-C levels were close to each other, after 12 weeks of treatment, LDL-C in the combined PCSK9 inhibitor group was significantly reduced and was safe and tolerable (Robinson, 2014). For patients with stable coronary heart disease, whether receiving high-intensity statin therapy or sub-high-intensity statin therapy and regardless of whether the baseline LDL-C level is <700 mg/L, PCSK9 inhibitors can continue to steadily reduce LDL-C levels (Koren, 2012).

3.2 Improve cardiovascular outcomes

A post-mortem analysis of the early phase II studies of evolocumab and alirocumab as PCSK9 inhibitors showed that patients treated with PCSK9 inhibitors had fewer cardiovascular events than those treated with placebo (Robinson, 2015; Sabatine, 2015). The cardiovascular outcome trial of PCSK9 inhibitors (FOURIER trial) compared the effects of evolocumab (140mg every two weeks or 420mg per month) or placebo on cardiovascular events in 27,564 patients with coronary artery disease (patients treated with statins and patients with LDL-C level of at least 70mg/dl). The level of LDL-C in patients treated with evolocumab decreased significantly (30mg/dl vs. 92 mg/dl). After 2.2 years of follow-up, patients treated with evolocumab had a significantly reduced risk of MACE (major adverse cardiovascular events) by 15%. There is a linear relationship between the LDL-C level achieved and the incidence of major adverse cardiovascular events (Sabatine, 2017). The ODYSSEY study showed that in 18924 patients who had developed acute coronary syndrome within 1 year, compared with placebo, alirocumab reduced the incidence of MACE in patients treated with statins. In the course of treatment, the level of LDL-C in the alirocumab group was lower. After a median follow-up of 2.8 years, the incidence of MACE decreased by 15%. Mortality was also lower in the alirocumab group (3.5% vs.4.1%).In addition, long-term use of PCSK9 inhibitors can reduce the risk of cardiovascular diseases, and the mortality rate of cardiovascular diseases is also reduced, which is statistically significant (O'Donoghue, 2022). The use of PCSK9 inhibitors not only reduces the risk of the first cardiovascular event but also reduces the risk of subsequent and recurrent events (Murphy, 2019). The benefits of PCSK9 inhibitors are directly proportional to the degree of LDL-C reduction, and further research shows that the use of these drugs to reduce lipoprotein (a) is independently related to its clinical benefits (O'Donoghue, 2019; Bittner, 2020).

3.3 Anti-inflammation

In vitro and in vivo studies have shown that PCSK9 is closely related to inflammation, and PCSK9 inhibitors may play an anti-inflammatory role. Marfella et al. and other scholars evaluated the anti-inflammatory effects of PCSK9 inhibitors in patients undergoing carotid endarterectomy. The results showed that PCSK9 inhibitors effectively decreased the expression of NLRP3(NOD-like receptor family, pyrin domain containing 3) inflammatory bodies and caspase-1(cysteinyl aspartate specific proteinase1) proteins, as well as the levels of IL-1 β(Interleukin-1β), TNF-α(Tumor necrosis factor-alpha)and NF-κB（nuclear factor kappa-B） proteins (Marfella, 2023). This study suggests that patients treated with PCSK9 inhibitors have a lower specific inflammatory load

in plaques than patients treated with OLLD(other lipid-lowering drugs). Since the inflammatory reaction in the vascular wall is considered to be directly proportional to the level of LDL-C (Willerson, 2004), they compared the expression of inflammatory proteins in patients with LDL-C<100 mg/dl. In these LDL-C matched subgroups, compared with patients treated with OLLD, patients treated with PCSK9 inhibitors have a lower abundance of inflammatory proteins in plaques. Studies conducted by Susan Kühnast et al. in a mouse model of FH(Familial Hypercholesterolemia) have shown that alirocumab reduces the adhesion of large monocytes to vascular endothelium by reducing ICAM-1(intercellular cell adhesion molecule-1) in endothelial cells (Kuhnast, 2014). In addition, the study showed that alirocumab reduced other markers of vascular inflammation, including T cell abundance in the aortic root, as well as diseased macrophages, necrotic contents, and cholesterol crystals. Studies by Bernelot M S et al. in patients with FH have shown that PCSK9 monoclonal antibodies reduce CCR2 (cell surface chemokine receptor 2) expression, migration capacity, and lipid accumulation in monocytes (Bernelot, 2017). This study found that inflammation-promoting factors were down-regulated, and the inflammation-inhibiting factor IL-10 (Interleukin-10) was up-regulated. Another study showed that PCSK9 siRNA inhibits the formation of PCSK9 and IL-1α (Interleukin-1α), IL-6 (Interleukin-6), and TNF-α, which are involved in atherosclerosis, by inhibiting nuclear translocation of NF-κB (Tang, 2012).

3.4 Reduce oxidative stress

Studies have shown that there is a link between PCSK9 and oxidative stress, so inhibition of PCSK9 may play a role in reducing oxidative stress (Cammisotto,2022). Cammisotto V et al. (2021) reported that evolocumab, a PCSK9 inhibitor, can reduce the serum ox-LDL (oxidized low density lipoprotein) concentration in patients with heterozygous FH (a homozygous gene in patients with familial hypercholesterolemia has heterozygous mutation and produces half of LDL-R with normal structure and function) .evolocumab can counteract the damage of HUVECs (Human Umbilical Vein Endothelial Cells) induced by hydrogen peroxide (Safaeian, 2022). Alessia Silla et al. showed that treatment with the PCSK9 inhibitor evolocumab improved vascular oxidative stress and arterial stiffness in patients with hypercholesterolemia and high cardiovascular risk (Silla, 2023). Therefore, PCSK9 inhibitors may provide a therapeutic strategy for reducing cardiovascular risk associated with oxidative stress.

3.5 Protect vascular endothelium

PCSK9 inhibitors play an important role in protecting vascular endothelial cell function. The study results of Kong N et al. showed that Infoxlon sodium exerts its anti-atherosclerotic function mainly by inhibiting the activation of NLRP3 induced by ox-LDL(oxidized low density lipoprotein) and then blocking the activation of apoptosis-related granuloid protein (ASC) and caspase-1, thus blocking the mature form of inflammatory cytokines, and ultimately inhibiting endothelial cell pyrogenesis (Kong, 2022). Studies by Marques P et al. showed that PCSK9 inhibition alleviates systemic inflammation and endothelial dysfunction by limiting leuco-endothelial interactions. PCSK9 blocking may constitute a new therapeutic approach to control the inflammatory state associated with FH and prevent further cardiovascular events resulting from this cardiometabolic disorder. The study of Diminoa et al. (2020) observed that the endothelial function of FH patients was improved after treatment with evolocumab, which may be related to the decrease of low density lipoprotein, and further research is needed to investigate the potential mechanism. Clinical studies conducted by Schremmer J et al. (2023) in patients with coronary heart disease showed that 6 months of PCSK9 inhibitor treatment improved endothelial function and peripheral microcirculation while reducing arterial stiffness. Although PCSK9 inhibitors have shown good prospects in protecting vascular endothelial function, more research is needed to explore their effects and mechanisms in improving vascular endothelial function.

4 Applications in other diseases

4.1Kidney disease

PCSK9 inhibitors not only play an important role in the treatment of cardiovascular diseases but also provide a new possibility for the treatment of patients with kidney diseases. Zhang S et al. (2022) found that for patients with coronary heart disease complicated with impaired renal function, the combined application of PCSK9 inhibitors is beneficial to improve the blood lipid compliance rate of patients. Research by Skeby C K et al. (2023) suggests that PCSK9 inhibition can reduce proteinuria in patients with kidney disease to a certain extent.CI-AKI (Contrast-Induced Acute Kidney Injury) is a serious complication caused by intravascular contrast media. Yu Ma et al. (2022) investigated the potential effects of PCSK9 inhibitors on the prevalence of CI-AKI after PCI (Percutaneous Coronary Intervention). The results showed that the incidence of CI-AKI was lower in the PCSK9 inhibitor group, which indicated that the PCSK9 inhibitor had a protective effect on CI-AKI. At the same time, their research shows that PCSK9 inhibitor combined with hydration and statins therapy is an effective method to prevent CI-AKI.

4.2 Cerebrovascular disease kidney disease

In addition to the recognized cardiovascular protective effect, PCSK9 inhibitors also show a role in cerebrovascular protection, providing a new possibility for the treatment of patients with cerebrovascular diseases. A meta-analysis showed that the addition of PCSK9 inhibitors reduced the relative risk of stroke by 26% compared with the placebo group, and this effect was not affected by previous stroke history or baseline LDL-C levels. At the same time, the analysis also proved that PCSK9 inhibitors were safe and did not increase the risk of hemorrhagic stroke (Sagris, 2021). Robert P Giugliano et al. (2020) carried out a further analysis of the

FOURIER trial. Based on stroke history, they analyzed the efficacy of evolocumab in reducing overall stroke and stroke subtypes. It turns out that Inhibition of PCSK9 with evolocumab added to statin in patients with established atherosclerosis reduced ischemic stroke and cardiovascular events in the total population and in key subgroups, including those with prior ischemic stroke. A recent meta-analysis found that PCSK9 inhibitors can reduce levels of LDL-C and Lpa(Lipoprotein a) and reduce the risk of stroke without increasing the risk of mortality or adverse neurological events. The meta-analysis also showed that the effect of PCSK9 inhibitors on stroke could not be fully explained by the decrease in LDL-C (Moustafa, 2024).

5. Conclusions

More and more studies have found that PCSK9 inhibitors have a variety of pleiotropic effects beyond lipid-lowering, including improving cardiovascular outcomes, anti-inflammation, reducing oxidative stress, and improving vascular endothelial function. However, the PCSK9 inhibitors currently available for clinical application are limited and far from meeting clinical needs. We need more research to further develop PCSK9 inhibitors that are safer and more effective for the human body to meet clinical needs. In addition, PCSK9 inhibitors are not only beneficial to the treatment of cardiovascular diseases but also provide a new possibility for the treatment of patients with renal disease and cerebrovascular diseases. Other disease fields can also appropriately refer to evidence-based medical evidence, clinical practice experience, and basic research on PCSK9 inhibitors in the field of cardiovascular diseases, with a view to further expanding the scope of clinical use of PCSK9 inhibitors.

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