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PCSK9 inhibitors – new era of dyslipidemia treatment - effectiveness in reducing low-density lipoprotein (LDL-C) and cardiovascular risk

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Abstract

Introduction: Abnormal blood cholesterol levels in patients with increased cardiovascular risk have a worse prognosis for patient survival. Treating dyslipidemia is important because it can improve patient comfort and safety. It sometimes happens that currently used drugs to lower cholesterol are not effective - patients develop tolerance or experience serious side effects. For this reason, scientists are looking for new drugs with a different mechanism of action. An example of such a group of drugs are PCSK9 inhibitors used to treat dyslipidemia. In this paper, we will look at the effectiveness of currently used PCSK9 inhibitors, but also at the potential risks associated with their use.

Material and methods: We searched for materials for this work in the Pubmed and Google Scholar databases using the keywords: "dyslipidemia", "cardiovascular disease", "PCSK9 inhibitors", "statins". Then we analyzed the selected materials.

Aim of the study: Evaluation of the

Conclusion: PCSK9 inhibitors are drugs that are very effective in lowering low-density lipoprotein (LDL-C), while reducing cardiovascular risk and potentially having long-lasting effects. Scientists are looking for new PCSK9 inhibitors with different mechanisms of action, which will be an even more effective therapy in lowering LDL-C.

Keywords:
PCSK9 inhibitors; cardiovascular disease; dyslipidemia

Introduction

Dyslipidemia and hyperlipidemia, understood as a disturbance of the lipid balance in the body, is one of the main risk factors for the development of cardiovascular diseases, which cause a significant number of deaths around the world. An abnormal lipid profile, including increased levels of low-density cholesterol (LDL-C), triglycerides, and decreased levels of high-density lipoprotein (HDL) contributes to the process of atherosclerosis [1], leading to serious complications such as myocardial infraction [2] or stroke [3]. In response to this

global health problem, the management of dyslipidemia has evolved from simple lifestyle recommendations to advanced pharmacological therapies that target a variety of metabolic pathways to optimize the lipid profile. In recent years, the development and implementation of new drugs, such as Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors, farnesoid X receptor (FXR) agonists and drugs that reduce cholesterol absorption, have contributed to significant progress in treatment. These innovations, supported by in-depth genetic and molecular research, have enabled a more personalized approach to therapy for patients with dyslipidemia. Despite these advances, challenges remain, including drug resistance, drug interactions, and differences in therapeutic response among diverse population groups. Furthermore, there is a growing understanding that a comprehensive approach, combining lifestyle modification and pharmacotherapy, is crucial for the effective management of dyslipidemia. This work aims to thoroughly examine the latest developments in the treatment of dyslipidemia, analyzing current therapeutic options and assessing their effectiveness, safety and impact on patient health.

Epidemiology of dislipidemia

Recent studies have provided a deeper understanding of dyslipidemia's global trends and implications. The NCD-RisC study, involving over 100 million individuals from various countries, shows significant geographical differences in cholesterol levels, indicating varying impacts of public health interventions across regions. In high-income Western countries and Singapore, notable reductions in non-HDL cholesterol levels have been observed since 1980, reflecting successful health policy implementations [4].

Another study focusing on young adults highlights a concerning prevalence of dyslipidemia, particularly among those over 30 years of age. This age group shows a sharp increase in dyslipidemia prevalence, with risk factors like overweight and obesity contributing significantly to this trend. The study suggests a need for early intervention strategies targeting younger populations to prevent long-term cardiovascular risks [5].

Risk factors and complications of hyperlipidemia

Hyperlipidemia, which is characterized by elevated levels of lipids in the blood, has numerous causes that can be broadly categorized into genetic factors, lifestyle choices, and other underlying conditions.

a) Genetic Factors:

- Familial Hypercholesterolemia (FH): This inherited disorder is marked by high levels of total cholesterol and LDL-C from birth, leading to early onset of cardiovascular diseases. It results from mutations in genes responsible for cholesterol metabolism, such as the LDL receptor (LDLR) gene, the PCSK9 gene, and the apolipoprotein B (apo B) gene [6]

b) Lifestyle Factors:

- Diet: Consuming foods rich in saturated fats, trans fats, and cholesterol can significantly raise blood lipid levels. Diets high in simple sugars also contribute to elevated triglycerides [6]
- Physical Inactivity: Lack of exercise is linked to increased levels of LDL-C and decreased levels of HDL-C, contributing to hyperlipidemia [7]
- Smoking: Smokers generally have higher levels of total cholesterol, triglycerides, and LDL-C, along with lower levels of HDL-C compared to non-smokers [8]

c) **Other Medical Conditions and Medications:**

- Metabolic Disorders: Conditions like type 2 diabetes and obesity are often associated with abnormal lipid profiles, including high triglycerides and LDL-C, and low HDL-C levels [9]
- Liver and Kidney Diseases: Disorders affecting the liver or kidneys can disrupt normal lipid metabolism, leading to hyperlipidemia [6]
- Hypertension [6]
- Hypothyroidism [6]
- Medications: Some drugs, including diuretics, beta-blockers, retinoids, corticosteroids, and immunosuppressants, can affect blood lipid levels, causing an increase in cholesterol [10]

Abnormal levels of lipids in the blood can lead to many complications - especially those related to the cardiovascular system. Dyslipidemia is a major factor in stroke. High LDL-C levels are closely associated with the risk of ischemic stroke [11]. High levels of LDL-C and lipoprotein a are also involved in pathogenesis of Coronary Crtery Disease (CAD) [12]. Peripheral arterial disease reduces the quality of life of patients and may even result in amputation, and the resulting atherosclerosis is another example of complications of dysilipidemia [13].

Familiar hypercholesterolemia

Familiar hypercholesterolemia (FH) is a disease inherited mainly in an autosomal dominant manner through a mutation in the gene encoding the LDL-receptor.[14] It is characterized by persistently elevated blood levels of LDL-C and an increased lifelong burden of cardiovascular disease.[14] Worldwide, the number of people suffering from FH exceeds 13 million, while in the United States alone there are over 600,000 patients.[15] The typical symptoms of FH are:: eyelid xanthomas, Achilles tendon xanthomas, xanthoma nodosa, corneal limbus senile and enlarged liver.[14] Early diagnosis and appropriate treatment are key to managing cardiovascular risk in patients with FH. Stratifying FH patients based on LDL-C levels and other risk factors may help improve disease management. [16]

PCSK9 inhibitors – a new generation of cholesterol-lowering drugs

Treatment of dyslipidemia involves both lifestyle changes and pharmacological treatment (statins, ezetimibe, fibrates). Increasing physical activity and reducing body weight is the basis for reducing abnormal cholesterol.[17], [18] Statins are the first group of drugs used to treat dyslipidemia. They work through selective blocking of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) causing a reduction in cholesterol biosynthesis and reducing its concentration. Despite the very good effect of their use, they may cause side effects. The most dangerous of them is rhabdomyolysis (breakdown of striated muscles).[19] Ezetimibe works by inhibiting the intestinal absorption of exogenous dietary and biliary cholesterol. Rhabdomyolysis (striated muscle breakdown).[20] Fibrates lower triglyceride levels and increase high-density lipoprotein (HDL) levels in the blood.[18], [21] In the case of any drug, intolerance or side effects may occur, which is why scientists are looking for new substances.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors are a class of medications used to lower low-density lipoprotein cholesterol (LDL-C) levels, which significantly reduces the risk of cardiovascular diseases. These drugs function by targeting the PCSK9 protein, which is crucial in cholesterol metabolism. PCSK9 is an enzyme predominantly produced in the liver. It binds to LDL receptors (LDL-R) on the surface of liver cells and promotes their breakdown in lysosomes. This process decreases the number of LDL receptors available to clear LDL-C from the blood, resulting in elevated LDL-C levels .[22] Currently available medications are evolocumab, alirocumab and inclisiran.

There are several ways to inhibit PCSK9:

- Monoclonal Antibodies (Alirocumab and Evolocumab): These inhibitors are antibodies that attach to PCSK9, preventing its interaction with LDL receptors. This increases the recycling of LDL receptors back to the liver cell surface, enhancing the removal of LDL-C from the bloodstream. This mechanism can lower LDL-C levels by about 55-60% [23]
- Antisense Oligonucleotides (ASOs): These bind to the mRNA of the PCSK9 gene, inhibiting its expression through Watson-Crick base pairing, thereby reducing PCSK9 protein levels.[23], [24]
- siRNAs: Small interfering RNAs interfere with the degradation of specific mRNA sequences, thus inhibiting PCSK9 gene expression and the synthesis of the corresponding protein.[23], [25]
- CRISPR/Cas9: This gene-editing technology induces double-strand breaks in DNA, leading to error-prone repair and reduced expression of the PCSK9 gene [23], [26]
- BMS-962476: These compounds prevent the binding of PCSK9 to LDL-R, disrupting the degradation process and increasing the recycling and circulation of LDL receptors, which enhances LDL uptake and lowers LDL-C levels [27]

Inhibitors PCSK9 are primarily intended for patients who have specific needs in managing their cholesterol levels, particularly those who:

- Do Not Achieve Target LDL-C Levels with Statins: Patients who are on the maximum tolerated doses of statins but still do not reach their target LDL-C levels can benefit from the addition of PCSK9 inhibitors. Clinical trials, such as the FOURIER and ODYSSEY OUTCOMES studies, have shown that PCSK9 inhibitors significantly reduce LDL-C levels and improve cardiovascular outcomes in these patients [28]
- Are Statin-Intolerant: Some patients experience adverse effects from statins, such as muscle pain or weakness, which prevent them from using these drugs. For these individuals, PCSK9 inhibitors offer an alternative method to lower LDL-C without the side effects associated with statins [29]
- Have Very High Cholesterol Levels: Patients with familial hypercholesterolemia, a genetic condition characterized by extremely high levels of LDL-C, can benefit greatly from PCSK9 inhibitors. These medications can help reduce LDL-C levels when other treatments are insufficient [30]
- Are at High Risk for Cardiovascular Events: Individuals with a history of cardiovascular events, such as heart attacks or strokes, or those with high-risk factors for such events, may use PCSK9 inhibitors to further reduce their risk. The inhibitors have been shown to decrease the likelihood of

future cardiovascular incidents by significantly lowering LDL-C levels and contributing to the stabilization of atherosclerotic plaques [31]

PCSK9 inhibitors provide an effective treatment option for patients who need additional help in managing their cholesterol levels beyond what statins can offer, or for those who cannot tolerate statins.

Evolocumab and alirocumab - monoclonal antibodies

The effectiveness of evolocumab and alirocumab in the prevention of cardiovascular events is assessed in many clinical trials. The FOURIER-OLE study demonstrated the high potential of Evolocumab in lowering LDL-C levels. From the initial LDL-C values (median 91 mg/dL), patients treated with Evolocumab managed to achieve a decrease in LDL-C to a median level of 29 mg/dL. Moreover, only 12 weeks of therapy were enough for the LDL-C level to drop by an average of 58.4%.[32] In the light of the currently applicable guidelines for the management of dyslipidemia[33], the effects of evolocumab look promising. It was also shown that patients who started Evolocumab therapy earlier (especially during the first three years of treatment) had a lower risk of cardiovascular death.[32] In addition to LDL-C, Evolocumab also reduced other atherogenic markers such as non-HDL (50.2% decrease) and apolipoprotein B (44.4% decrease).[32] The HUYGENS study aimed to determine the effect of evolocumab on atherosclerosis. The LDL-C level dropped from 140.4 to 28.1 mg/dL.[34] The main measure of vascular changes was fibrous cap thickness (FCT) determined by optical coherence tomography (OCT) measurements. FCT improved by as much as 42.7 μm in the Evolocumab-treated group, while in the placebo group only by 21.5 μm. [34] In the case of Alirocumab, FCT was on average 62.67 μm compared to 33.19 μm with placebo.[35] More stable atherosclerotic plaques are more resistant to rupture, therefore reducing the risk of acute cardiovascular events. Regression of atherosclerotic plaques is confirmed by the GLAGOV study. Percent atheroma volume (PAV) and normalized total atheroma volume (TAV) were used to monitor vascular changes. In the Evococumab-treated group, both parameters improved (decrease in PAV by 0.95% vs. increase by 0.05% in the placebo group; decrease in normalized TAV by 5.8 mm3 vs. decrease by 0.9 mm3 in the placebo group), indicating a lower risk of cardiovascular events.[36] Scientists also examined the effect of Evolocumab on modulating inflammation. This medicine may affect the properties of circulating immune cells. Moreover, the importance of advanced profiling of these cells under stress is emphasized, which allows for a deeper understanding of their role in the context of atherosclerotic cardiovascular disease. Such profiling allows for a more precise

determination of the phenotypic differences of immune cells and their response to stress, which is crucial to better understand the connections between inflammatory processes and cardiovascular diseases. These results open a new perspective on the mechanisms by which PCSK9-targeted therapies influence the immune system and their potential link to heart disease.[37] The ODYSSEY study examined the effectiveness of alirocumab in patients who survived acute coronary syndromes. The LDL-C value from the initial mean value of 92±31 mg/dL after 4, 12 and 48 months of alirocumab therapy was 40 mg/dL, 48 mg/dL and 66 mg/dL, respectively, while in the placebo group it was 93 mg/dL, 96 mg/dL and 103 mg/dL. A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died during the experiment. It was shown that the risk of ischemic cardiovascular events was lower after the use of alirocumab.[38]

Inclisiran

Inclisiran is a medicine that uses small interfering RNA (siRNA) technology to lower the level of low-density lipoprotein cholesterol (LDL-C) in the body. It introduces siRNA into liver cells, which binds to PCSK9 mRNA, leading to its degradation and preventing the production of PCSK9 protein.[39] Inclisiran was approved for use in the EU in December 2020.[25] The results of analyzes regarding inclisiarn indicate equally high effectiveness in lowering LDL-C with much less frequent dosing compared to other PCSK9 inhibitors. In the ORION-10 and ORION-11 studies, the LDL-C level decreased by 51.3% and 45.8%, respectively, compared to the placebo groups, where the LDL-C level increased by 1% and 4%, respectively. After treatment with inclisiaran, the concentrations of total cholesterol, non-HDL cholesterol and apolipoprotein B also decreased, while the level of HDL-C increased.[40] The dose of the drug may also be important. This was investigated in the ORION-15 study, which used three different doses of inclsiran sodium (300 mg, 200 mg, 100 mg). After 180 days from the start of therapy, the greatest placebo-corrected reductions in LDL-C and PCSK9 protein were observed in patients taking 300 mg of inclisiran sodium (65.3% and 79.2%, respectively), and the smallest in patients taking 100 mg of inclisiran sodium 100 mg (56.6% and 66.3%, respectively), however, regardless of the dose, the treatment turned out to be effective. [41] The first study that attempted to evaluate long-term treatment with inclisiran in patients with high cardiovascular risk was the ORION-3 study, i.e. the extended ORION-1 study. LDL-C levels decreased after inclisiran treatment to 47.5% at

day 210. Moreover, patients who continued treatment maintained low LDL-C levels for 1,440 days. It should be mentioned that patients received inclisiran twice a year.[42]

Genetic engineering - the future of dyslipidemia treatment

Scientists are still looking for new PCSK9 inhibitors with a different mode of action than the drugs currently approved for use. CRISPR and Cas (CRISPR-associated) genes is an adaptive immune system of microorganisms based on clustered regularly interspaced short palindromic repeats (CRISPR). Its action takes place in three stages: adaptation, expression and interference. Adaptation involves the interference of short DNA fragments at CRISPR locus. Then, in the expression stage, a long primary transcript of the CRISPR loci (pre-crRNA) is created and processed into short crRNA. During interference, foreign DNA or RNA is cut. CRISPR/Cas systems are divided into three types, of which type II requires the use of the Cas9 protein to create crRNA and cut the target DNA.[43] The CRISPR base editor method allows to modify the genome by replacing one base pair with another, which allows new drugs to permanently disable the production of, for example, the PCSK9 protein.[44] In the case of the PCSK9 gene, this modification concerns adenine and thymine into guanine and cytosine. The effectiveness of such a replacement in the tested animals (approx. 60% of the edit) resulted in a decrease in the PCSK9 protein in the blood by approximately 90%, which translated into a decrease in LDL-C levels by approximately 60%.[45] However, it has not been confirmed how long this effect will last. The durability of the effect was checked in the case of the experimental drug VERVE-101, acting on the same principle, performed on animals, showing an average decrease in the level of PCSK9 protein by 67% and 83% (depending on the dose of VERVE-101 0.75 mg/kg and 1.5 mg/kg). . The reduction of this protein persisted until day 476. Reducing PCSK9 protein expression affected LDL-C levels. Reductions of 46% and 70% were achieved (depending on the dose of VERVE-101 0.75 mg/kg and 1.5 mg/kg). A transient increase in alanine and aspartate aminotransferase was also observed after drug administration, which disappeared by day 14. However, the total bilirubin level remained normal. This means that the drug is well tolerated. This study allowed further analysis of the drug, this time in patients with heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease.[44]

Discusion

PCSK9 inhibitors, as a new group of drugs, have a clear impact on the improvement of lipid parameters - a decrease in LDL-C, non-HDL-C, triglycerides and an increase in HDL-C especially in patients with familial hypercholesterolemia. Controlling the level of these indicators is very important in the prevention of cardiovascular diseases. The effectiveness of inclisiran does not differ significantly from that of evolocumab and alirocumab, but the dosage of these preparations should be mentioned. An undoubted advantage of inclisiran for patients suffering from cardiovascular diseases is the less frequent administration of the preparation. Inclisiran should be administered as a single subcutaneous injection administered: first time, again after 3 months and then every 6 months, evolocumab once every two weeks (140 mg) or once a month (420 mg), and alirocumab also every two weeks. Despite the good effect of PCSK9 inhibitors on metabolic parameters, attention should be paid to the side effects of these drugs. Most frequently reported were muscle pain (27.2 %), back pain (12 %), nasopharyngitis (9.3 %), headache (9.2 %), upper respiratory tract infections (9 %), flu-like symptoms (7.5 %), joint pain (7 %) or an increase in alanine or aspartate aminotransferase levels three times above the upper limit of normal (6 %)[46]. There have also been disturbing reports suggesting that PCSK9 inhibitors may have harmful neurocognitive effects and may induce diabetes. Cognitive impairment after the use of evolocumab was checked in the EBBINGHAUS study. There were no significant differences between the evolocumab and placebo groups in cognitive function over a mean period of 19 months.[47] The diabetes-inducing effect of PCSK9 inhibitors was denied in the studies FOURIER [48], OSLER-1 [49]. PCSK9 inhibitors have no effect on glucose metabolism.[46] Genetic engineering in the form of the CRISP/Cas method may prove to be the future of dyslipidemia treatment. Permanent modification of the genome allows for long-term exclusion of the expression and production of the PCSk9 protein, which will affect the level of LDL-C. Because such drugs are still being developed, we do not yet know their effects on human patients. Much more research is needed to investigate side effects.

Conclusion

PCSK9 inhibitors are widely used in the treatment of dyslipidemia. Few serious side effects confirm the safety of their use. Reducing the cardiovascular risk after using them is

associated with a lower percentage of patients requiring hospital treatment and increases their quality of life. However, further scientific research is needed to determine which of the PCSK9 inhibitors have the longest effect.

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