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Evolution of Pharmacotherapy for Hypercholesterolemia: Efficacy and Adverse Effect Profile from Bile acid sequestrants to Modern Molecular Therapies

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Abstract

Dyslipidemia, particularly elevated levels of low-density lipoproteins (LDL), plays a key role in the pathogenesis of atherosclerosis and its cardiovascular complications**.** The aim of this paper is to present the evolution of therapeutic strategies aimed at reducing LDL- C levels, with particular emphasis on modern molecular therapies [1]. Mechanisms regulating lipid metabolism are discussed, including the role of the LDL-LDLR-PCSK9 axis [2]. Classical treatment methods, such as bile acid sequestrants, statins, and ezetimibe, as well as newer therapeutic options, including bempedoic acid, PCSK9 inhibitors, and siRNA-based therapies, are presented. Future directions in pharmacotherapy, such as CETP inhibitors, evinacumab, and gene therapies using CRISPR-Cas9 technology, are also addressed. Modern treatment strategies enable significant reduction of LDL-C levels and a more precise therapeutic approach. Their use aligns with the development of personalized medicine, although further evaluation of long-term safety is required [3,4].

Keywords: Hypercholesterolemia, LDL, Statin, siRNA, Gene Therapies, Evinacumab.

INTRODUCTION

Abnormalities in lipoprotein metabolism constitute one of the key mechanisms underlying the development of cardiovascular diseases. With increasing industrialization and the rising consumption of highly processed foods, dyslipidemia has become an increasingly significant clinical issue. Low-density lipoproteins (LDL), responsible for transporting

cholesterol to peripheral tissues, play a particularly important role. Disturbances in LDL homeostasis, including both increased synthesis and impaired catabolism, lead to their accumulation in the vascular wall and the initiation of atherogenic processes. These processes may remain asymptomatic for a long time, posing a significant diagnostic and clinical challenge. At the same time, numerous studies demonstrate a strong correlation between LDL levels and the risk of cardiovascular events [5,6].

Therefore, therapeutic strategies aimed at modulating LDL metabolism and reducing its concentration in the blood are of particular importance. Contemporary approaches to the treatment of hypercholesterolemia include both classical pharmacological interventions and modern therapies based on molecular mechanisms. A clear evolution of therapeutic strategies toward personalized medicine is observed, taking into account the individual cardiovascular risk of the patient. According to current scientific guidelines, treatment focuses on achieving target LDL-C levels, which are determined based on the degree of cardiovascular risk. The aim of this paper is to present the evolution of treatment methods for hypercholesterolemia, with particular emphasis on modern molecularly targeted therapies [6,7].

Materials and methods

This study employed a narrative literature review methodology focused on the evolution of pharmacotherapy in hypercholesterolemia. The analysis was conducted based on scientific publications indexed in PubMed and Google Scholar. The search strategy included the following keywords: “hypercholesterolemia”, “dyslipidemia”, “statins”, “PCSK9 inhibitors”, “inclisiran”, “bempedoic acid”, “LDL cholesterol”, and “atherosclerosis”. Publications published between 2003 and 2025 were included in the analysis, comprising original studies, narrative reviews, meta-analyses, and clinical trials related to the treatment of lipid disorders. The review included studies describing both conventional lipid-lowering agents, such as statins, ezetimibe, and bile acid sequestrants, as well as novel therapeutic approaches involving PCSK9 inhibitors, siRNA-based therapies, CETP inhibitors, and CRISPR technologies. The selected publications were subjected to qualitative analysis in order to present the evolution of pharmacological strategies in the treatment of hypercholesterolemia.

1. Physiology and Pathophysiology of Hypercholesterolemia

Cholesterol in the blood is transported in the form of lipoproteins due to its hydrophobic nature. Physiologically, the body maintains a balance between endogenous cholesterol synthesis, intestinal absorption, and clearance from circulation. This process is regulated by feedback mechanisms-an increase in intracellular cholesterol inhibits its synthesis and enhances storage, whereas its deficiency increases LDL receptor expression and promotes cholesterol uptake from plasma [8]. Low-density lipoproteins (LDL) participate in cholesterol transport in plasma, ensuring its delivery to extrahepatic tissues. A key structural component is apolipoprotein B-100, which enables binding to LDL receptors on the surface of cells. Excess LDL leads to its accumulation in the vascular wall, where - due to its pro-inflammatory properties - it activates the endothelium and promotes phagocytosis by macrophages. Consequently, foam cells are formed and LDL oxidation occurs, which represents a key stage in the development of atherosclerotic lesions.

The body possesses numerous mechanisms regulating LDL concentration, among which LDL receptors (LDLR) located on hepatocytes play a central role. After binding of the lipoprotein to the receptor, endocytosis occurs, followed by degradation of LDL particles, while the receptor returns to the cell surface. Disruptions of this mechanism, resulting from genetic mutations or alterations in post-translational regulation, lead to LDL accumulation in plasma [9,10]. Hypercholesterolemia may be primary (genetically determined) or secondary, associated with diet, metabolic diseases, or lifestyle factors.

An important role in regulating this pathway is also played by the PCSK9 protein, which binds to the LDL receptor and directs it toward intracellular degradation. As a result, the number of LDL receptors on the surface of hepatocytes decreases, limiting LDL uptake and increasing its concentration in the blood. Processes leading to increased LDL levels in plasma and their deposition in the vascular wall, accompanied by an inflammatory response, are largely associated with disturbances in the LDL-LDLR-PCSK9 axis. This pathway currently represents one of the key targets of lipid-lowering therapies [8,11].

2. Evolution of Pharmacotherapy for Hypercholesterolemia

2.1. Bile Acid Sequestrants

Bile acid sequestrants were introduced into clinical practice in the early 1970s as the first effective cholesterol-lowering drugs. Their introduction represented a major milestone in the prevention of cardiovascular diseases. Initially, cholestyramine was used, followed by the development of colestipol and colesevelam [12]**.** Their mechanism of action involves binding bile acids in the intestinal lumen, leading to their increased excretion in feces. In response to the reduced bile acid pool, the liver increases their synthesis, utilizing intracellular cholesterol. This results in increased expression of LDL receptors on hepatocytes and enhanced LDL uptake from the blood, leading to a reduction in their plasma levels.

The efficacy of this group of drugs in reducing LDL levels is approximately 15-30%. Their use is limited by adverse effects such as gastrointestinal disturbances and impaired absorption of fat-soluble vitamins A,D,E,K and certain medications, including thyroxine, thiazide diuretics, and vitamin K antagonists. These limitations significantly contribute to poor patient adherence to therapy [13].

2.2. Statins

Statins represent a breakthrough in the treatment of hypercholesterolemia. Introduced in the 1980s, they were the first to demonstrate a significant reduction in mortality and cardiovascular events. The first representative was Lovastatin (currently used less frequently due to its short half-life and lower ability to reduce LDL levels). At present, the most commonly used statins are Atorvastatin and Rosuvastatin, the latter being characterized by the strongest lipid-lowering effect. The primary mechanism of action of statins is the inhibition of HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. This inhibition leads to increased expression of LDL receptors on hepatocytes and enhanced LDL uptake from the blood, resulting in reduced plasma LDL levels [14].

The effectiveness of statins has been confirmed in numerous meta-analyses, demonstrating a 40% reduction in all-cause mortality and a 25% reduction in cardiovascular events. Moreover, statins exhibit pleiotropic effects, including stabilization of atherosclerotic plaques, anti-inflammatory activity, and improvement of endothelial function [15]**.** Statins are generally well tolerated; however, they may cause adverse effects such as myalgia, myopathy, or a transient increase in liver enzyme activity, which are usually self-limiting disorders.

Therefore, in the presence of muscle symptoms, measurement of creatine kinase activity is recommended. There are also reports of a slight increase in the risk of developing type 2 diabetes. Nevertheless, the benefits of statin therapy clearly outweigh the potential risks, making them the cornerstone of hypercholesterolemia treatment [16].

2.3. Ezetimibe

Ezetimibe was introduced in the early 2000s as the first representative of selective cholesterol absorption inhibitors. Its mechanism of action involves inhibition of the NPC1L1 transporter located in the brush border of the small intestine. This leads to reduced intestinal absorption of cholesterol, which secondarily increases LDL receptor expression in the liver and enhances LDL clearance from the blood. Due to its distinct mechanism of action, ezetimibe is often used in combination therapy with statins.

The standard dose is 10 mg once daily, resulting in an approximate 15–20% reduction in LDL levels. In combination with a statin LDL-C reduction of 55% can be achieved, which is particularly important in patients at high cardiovascular risk. Ezetimibe has a favorable safety profile and represents a good alternative in patients with statin intolerance. The most common adverse effects include gastrointestinal disturbances [17,18].

2.4. Bempedoic Acid

Bempedoic acid was introduced into clinical practice in 2020. It is an oral prodrug and an inhibitor of ATP citrate lyase (ACL), an enzyme acting upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. Inhibition of this enzyme leads to decreased cholesterol synthesis in hepatocytes and increased LDL receptor expression. The efficacy of the drug is estimated at approximately an 18% reduction in LDL levels compared to baseline. The CLEAR Outcomes trial demonstrated a reduction in major cardiovascular events in high-risk patients, particularly those with statin intolerance. The drug can be used in combination therapy, especially with ezetimibe. Adverse effects include increased uric acid levels, tendinopathies, and an increased risk of gallstone disease [19].

2.5. PCSK9 Inhibitors

PCSK9 inhibitors represent an example of molecularly targeted therapy. This group includes monoclonal antibodies such as alirocumab and evolocumab, which bind to the PCSK9 protein, preventing its interaction with LDL receptors. As a result, degradation of LDL

receptors is inhibited, leading to an increased number of receptors on the surface of hepatocytes and enhanced LDL clearance from the bloodstream. This therapy allows for LDL-C reduction of up to 50–60%.

These agents are characterized by high efficacy and a favorable safety profile. They are primarily used in patients at high and very high cardiovascular risk who fail to achieve target LDL-C levels despite optimal standard therapy. A significant limitation remains the high cost of treatment [20,21].

2.6. siRNA-Based Therapies

Therapies based on small interfering RNA (siRNA) represent a modern approach to the treatment of hypercholesterolemia. The main representative of this group is inclisiran, which selectively inhibits PCSK9 synthesis at the mRNA level.

Following subcutaneous administration, siRNA is internalized into hepatocytes, where it is incorporated into the RISC (RNA-induced silencing complex), leading to degradation of PCSK9 mRNA and inhibition of its translation. As a result, the number of LDL receptors increases, and LDL-C levels are significantly reduced, by approximately 50%. The dosing regimen includes administration at baseline, at 3 months, and subsequently every 6 months, which improves treatment adherence. This therapy is used as an adjunct in patients at high cardiovascular risk. Long-term safety requires further investigation [22,23].

3. Future Therapies

3.1. Selective CETP Inhibitors

One of the most promising directions in the development of pharmacotherapy for hypercholesterolemia involves selective inhibitors of cholesteryl ester transfer protein (CETP). An example is obicetrapib, which inhibits CETP activity, thereby blocking the transfer of cholesteryl esters from HDL lipoproteins to apoB-containing lipoproteins, including LDL [24]. The therapeutic effect of this mechanism is a simultaneous reduction in circulating atherogenic lipoproteins and an increase in HDL-C concentrations. Phase II clinical trials demonstrated that 12-week treatment with obicetrapib resulted in a significant, dose-dependent reduction in LDL-C levels. At doses of 5 mg and 10 mg, the maximum median LDL-C reduction reached approximately 51% compared with placebo [25].

In the BROOKLYN trial, in which obicetrapib was administered at a dose of 10 mg for 52 weeks, sustained reductions in LDL-C and lipoprotein(a) [Lp(a)] concentrations were observed in patients at high cardiovascular risk. The safety profile was favorable, with the incidence of adverse events comparable to placebo. Reported events, including transient reductions in leukocyte and neutrophil counts, were reversible in nature [26].

3.2. Evinacumab

Evinacumab is a monoclonal antibody directed against angiopoietin-like protein 3 (ANGPTL3). Neutralization of ANGPTL3 results in increased activity of lipoprotein lipase and endothelial lipase, thereby enhancing the catabolism of triglyceride-rich lipoproteins and reducing the pool of LDL precursors. Consequently, a significant reduction in LDL-C concentrations is achieved. The best-established indication for evinacumab therapy is homozygous familial hypercholesterolemia. In a randomized phase III clinical trial, intravenous administration at a dose of 15 mg/kg every 4 weeks resulted in a mean LDL-C reduction of approximately 47% from baseline. The safety profile of the drug is favorable, with the most commonly reported adverse events including nasopharyngitis, influenza-like symptoms, dizziness, and nausea, while maintaining good overall treatment tolerability [27].

3.3. Gene Therapies

Gene therapies represent the most advanced and potentially groundbreaking approach to the treatment of hypercholesterolemia. Examples include therapies based on CRISPR-Case (Clustered Regularly Interspaced Short Palindromic Repeats) technology, such as VERVE-101 and VERVE-102. This strategy involves the delivery of messenger RNA (mRNA) encoding a gene-editing enzyme together with guide RNA (gRNA) into hepatocytes, enabling precise modification of the gene sequence encoding the PCSK9 protein. As a result of this modification, a premature STOP codon is introduced, leading to permanent gene inactivation.

The biological consequence is suppression of PCSK9 synthesis, an increase in LDL receptor expression, and a substantial reduction in LDL-C concentrations, reaching approximately 60% relative to baseline values. Current data suggest that the therapeutic effect may persist for at least several months following a single administration. Reported adverse events primarily include infusion-related reactions and transient elevations in liver enzyme activity. However, it should be emphasized that the currently available data originate from early-phase clinical trials conducted in relatively small patient populations. Despite these promising results, gene therapies are associated with potential risks, including

hepatotoxicity and the possibility of unintended genetic modifications (off-target effects), underscoring the need for further studies evaluating the long-term safety and efficacy of this therapeutic strategy [28,29].

CONCLUSIONS

Disorders of LDL metabolism play a fundamental role in the pathogenesis of cardiovascular diseases, and their regulation remains the primary therapeutic target. Conventional treatment modalities, such as statins and ezetimibe, constitute the cornerstone of therapy; however, their efficacy may be insufficient in high-risk patients. The development of molecularly targeted therapies, particularly PCSK9 inhibitors and siRNA-based agents, has significantly expanded the possibilities for LDL-C reduction and enabled the achievement of more stringent therapeutic targets. The introduction of novel agents, such as bempedoic acid, together with the ongoing development of experimental therapies, has further broadened the available treatment options. Current trends indicate a transition toward personalized medicine and potentially durable interventions, such as gene therapies. Despite these promising advances, continued safety monitoring and evaluation of long-term clinical outcomes remain essential.

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