New Therapeutic Approaches in Treatment of Dyslipidaemia

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Dyslipidaemia is a well-known risk factor for the development of cardiovascular disease. Traditional statin therapy remains the cornerstone therapeutic approach. Ezetimibe showed good but limited results when used in combination with statins. Bempedoic acid has been thoroughly studied in multiple clinical trials, with a reduction in LDL cholesterol by approximately 15%. The first approved monoclonal antibodies for the treatment of dyslipidaemia, PCSK9 inhibitors, are currently used as second-line treatment for patients with unregulated lipid levels on statin or statin combination therapy. A new siRNA molecule, inclisiran, demonstrates great potential, particularly concerning compliance, as it is administered twice yearly and pelacarsen, an antisense oligonucleotide that targets lipoprotein(a) and lowers its levels. Volanesorsen is the first drug that was designed to target chylomicrons and lower triglyceride levels, and olezarsen, the next in-line chylomicron lowering agent, is currently being researched. The newest possibilities for the treatment of dyslipidaemia are ANGPTL3 inhibitors with evinacumab, already approved by the FDA, and EMA for the treatment of familial hypercholesterolemia.

Keywords: dyslipidaemia ; bempedoic acid ; PCSK9 inhibitors ; pelacarsen ; ANGPTL3 inhibitors

1. Introduction

Dyslipidaemias are divided into primary or familial dyslipidaemias, or secondary to other conditions (such as diabetes mellitus, thyroid diseases, obesity, or an unhealthy lifestyle), the latter being more common [1]. Familial forms account for less than 2% of all dyslipidaemias. Primary dyslipidaemias are caused by a genetic defect of a single gene (monogenic) or multiple genes (polygenic) [2]. Almost 50 years ago, Donald S. Fredrickson and his colleagues recognized alternations of physiologic levels of plasma lipoproteins that paved the way for the first phenotypic classification of lipoprotein disorders, established by separating lipoproteins using density gradient ultracentrifugation (beta-quantification). According to this classification, dyslipidaemias are subdivided into five different categories. In type I, primary hyperlipoproteinemia or familial hyperchylomicronaemia, caused by lipoprotein lipase deficiency or altered Apo-CII, there is an abnormality of chylomicrons leading to triglycerides greater than 99 percentiles; it is very rare. In type IIa, familial hypercholesterolemia or polygenic hypercholesterolemia, there is an LDL receptor deficiency resulting in elevated LDL cholesterol together with a total cholesterol concentration greater than 90 percentile and often apolipoprotein B, greater than 90 percentile. The most common phenotype IIb, familial combined hyperlipidaemia, consists of an abnormality in LDL and very-low-density lipoprotein (VLDL) cholesterol, affecting total cholesterol and/or triglycerides more than 90 percentile, and apolipoprotein more than 90 percentile. Type III, familial dysbetalipoprotenaemia, caused by a defect in Apo E 2 synthesis, is a rare form in which there is an abnormality in VLDL remnants and chylomicrons, resulting in elevated IDL; total cholesterol and triglycerides are greater than 90 percentile. Familial hypertriglyceridemia, phenotype IV, is caused by increased VLDL production and decreased excretion, leading to total cholesterol and triglycerides greater than 90 percentile. Finally, type V or endogenous hypertriglyceridemia is characterized by abnormal chylomicrons and VLDL, and triglycerides are greater than 99 percentiles [2][3][4]. It is important to mention that the Fredrickson classification system does not address dyslipidaemias related to low HDL cholesterol or elevated Lp(a). For this and other reasons, this classification is no longer so commonly used, and dyslipidaemias are usually defined as those with elevated total and LDL cholesterol, those with elevated triglycerides, and those with both elevated LDL cholesterol and elevated triglycerides, with considerable attention also paid to elevated Lp(a) and low HDL cholesterol. In evaluation of primary dyslipidaemias, family history is of great importance, together with a physical examination which can often reveal xanthomas, deposits of lipids in the skin and sometimes subcutaneous tissue. Currently, secondary dyslipidaemias related to diabetes mellitus, obesity, an unhealthy lifestyle, and other medical disorders are the focus of interest because dietary and lifestyle modifications influence these conditions to a great extent.

Lipid-lowering therapy, primarily statins, also known as hydroxymethyl glutaryl coenzyme A reductase inhibitors, decrease vascular events including stroke and myocardial infarction and cause a reduction in all-cause mortality by 10% for every 1.0 mmol/L reduction in LDL-cholesterol levels [5]. Therefore, statins are well-established and widely recommended therapeutics, according to the guidelines of the European Society of Cardiology and the American Heart Association. Apart from statins, other therapeutics that reduce LDL levels have been shown to be effective in decreasing the risk of cardiovascular events. Ezetimibe binds to the NPC1L1 transporter protein and consequently inhibits intestinal absorption of cholesterol, and has a synergistic effect when combined with statins in reducing LDL cholesterol levels and thereby MACE (major cardiovascular events), as shown in the IMPROVE-IT and SHARP trials [6][7]. Adding proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to moderate- or high-intensity statin therapy regimens leads to cardiovascular risk reduction in patients with stable atherosclerotic cardiovascular disease, or after recent acute coronary syndromes [8][9]. These medicines inactivate proprotein convertase subtilsin/kexin type 9 (PCSK9), inhibiting the labelling of LDL receptors for degradation, thus prolonging LDL receptor activity at the cell membrane, leading to additional LDL cholesterol, lowering by 50% to 60% compared to statin monotherapy [10].

2. New Therapeutic Approaches in Treatment of Dyslipidaemia

2.1. Drugs Used in Dyslipidaemia

Statins

Statins became almost a synonym for the treatment of dyslipidaemia. These drugs are among the most widely used medications, with atorvastatin being one of the best-selling pharmaceuticals [11]. Statins have been in use for almost 50 years and are the first therapeutic choice for dyslipidaemia, particularly for elevated LDL cholesterol levels [12]. Current statins approved by the EMA include atorvastatin, simvastatin, rosuvastatin, fluvastatin, pitavastatin, lovastatin and pravastatin. They act as antagonists for 3-hydroxy-3-methylglutaryl coenzyme A reductase, and by inhibiting the enzyme HMG-3-CoA, reductase blocks the endogenic cholesterol synthase pathway, resulting in lower LDL cholesterol serum levels [13]. The main indication for statin treatment is a high serum cholesterol level and CVD. Studies have observed beneficial effects of statins on atherosclerotic plaques by stabilizing plaques and decreasing the risk of cardiovascular incidents [14]. Statins are generally well-tolerated drugs, but they have significant adverse effects, including myopathy and rhabdomyolysis. In addition, there is no doubt that long-lasting statin treatment results in de novo occurrence of type 2 diabetes mellitus (T2DM), particularly in subjects who have metabolic syndrome or are prone to T2DM.

Bempedoic Acid

Bempedoic acid is an adenosine triphosphate (ATP) citrate lyase inhibitor that inhibits cholesterol biosynthesis and increases LDL receptor expression. ATP citrate lyase is an enzyme upstream of HMG-CoA reductase in the biochemical cholesterol synthesis pathway. Inhibition of ATP citrate lyase prevents endogenous cholesterol synthesis and indirectly increases the expression of LDL receptors, thereby increasing the clearance of LDL cholesterol [15]. Bempedoic acid is a prodrug that requires activation, and the active metabolite ESP15228 inhibits ATP citrate lyase [16]. It is administered orally once a day at a dose of 180 mg and is approved by the FDA and EMA for the treatment of hypercholesterolemia [16][17]. Efficacy and safety of bempedoic acid have been evaluated in five clinical trials: HARMONY, WISDOM, SERENITY, TRANQUILITY and OUTCOMES. Currently, the OUTCOMES study is underway with a focus on the reduction in cardiovascular incidents and diabetes compared to patients on statin therapy [18].

Ezetimibe

Ezetimibe is a selective inhibitor of cholesterol absorption. The mechanism of action of ezetimibe is mediated by targeting the sterol transporter Neimann-Pick C1 Like 1 (NPC1L1), which is localized at the border cells in the small intestine. Binding to the transporter inhibits it and decreases the absorption of cholesterol, further decreasing cholesterol circulation through the liver, and finally increasing the clearance of cholesterol from blood [16]. It is orally administered at a daily dose of 10 mg. It is worth noting that the absorption of ezetimibe differs in younger and older adults, with older adults having greater exposure than younger adults. However, no dose correction was required in older adults [19]. The efficacy of ezetimibe is mostly observed in co-therapy with statins, with LDL cholesterol levels decreasing by 10 to 15%, varying with the different statin agents combined. More recent studies have shown great results in ezetimibe and bempedoic acid co-therapy, with a mean difference of 38% in LDL cholesterol levels compared to the placebo group. Ezetimibe monotherapy is also acceptable, especially in patients who do not tolerate statins and require modest LDL cholesterol level reduction, with results showing an 18% decrease compared to placebo patients [17][20]. The FDA and EMA approved ezetimibe and currently, there are fixed combinations of different statins with ezetimibe and fixed combinations of bempedoic acid 180 mg with ezetimibe 10 mg. Approval is for the treatment of hypercholesterolemia and mixed dyslipidaemia in patients at a

high risk of cardiovascular incidents with high LDL cholesterol levels. Ezetimibe has a good safety profile, with few to no adverse effects noted in the literature. The SEAS trial observed a potentially increased incidence of cancer in patients receiving ezetimibe therapy, but further trials found no significant difference [16][21].

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new generation of lipid-lowering drugs with many clinical trials suggesting very good LDL cholesterol-lowering results. PCSK9 plays an important role in LDL receptor downregulation. LDL receptors are found on hepatocytes and play a role in the removal of circulating LDL cholesterol from blood. When the PCSK9 protein binds to the LDL receptor, it starts the process of degrading the receptor, thus increasing LDL cholesterol levels. The monoclonal antibodies alirocumab and evolocumab inhibit PCSK9 binding to LDL receptors, increase recycling of LDL receptors, and indirectly lower circulating LDL cholesterol levels by increasing LDL cholesterol uptake [22]. The third monoclonal antibody in this drug class was bococizumab, but trials were discontinued because of immunogenicity and higher injection site reactions than in two aforementioned [16]. Both currently used monoclonal antibodies, alirocumab and evolocumab, are administered subcutaneously once every two weeks in doses starting from 75 mg to 300 mg depending on the initial LDL cholesterol levels and 140 mg, respectively. It is important to note that steady concentrations of alirocumab and evolocumab were achieved within 4–6 weeks from the start of the treatment [23][24]. Most insights on PCSK9 inhibitors were obtained in the ODYSSEY OUTCOMES trial of alirocumab and the FOURIER trial of evolocumab. The ODYSSEY OUTCOMES trial showed that alirocumab not only lowers circulating LDL cholesterol levels but also has a preventive effect on cardiovascular incidents [24]. The FOURIER trial observed a 15% decrease in cardiovascular incidents compared with the placebo group in patients receiving evolocumab therapy, who previously had major cardiovascular incidents and were on high-dose statin therapy [23].

Inclisiran

One of the most recently approved drugs for the treatment of dyslipidaemia is inclisiran. It is a small interfering ribonucleic acid (siRNA) that targets PCSK9. As mentioned earlier, PCSK9 is an important protein involved in LDL receptor degradation. Inclisiran, an siRNA, interferes with the translation of PCSK9 by cleaving messenger RNA, thereby decreasing PCSK9 production. The absence of PCSK9 results in the upregulation of LDL receptors and, consequently, lowers the circulating level of LDL cholesterol [25][26]. The biggest advantage of inclisiran is its administration scheme. Inclisiran is administered subcutaneously on days 1, day 90, day 180, and afterwards once every six months. The usual dosage is 284 mg in a single administration [25]. Efficacy of inclisiran was observed in ORION trials. These trials showed that LDL cholesterol levels were reduced by approximately 50% compared to placebo groups [17].

Pelacarsen

The discovery of lipoprotein(a) [(Lp(a)], and the fact that elevated Lp(a) is an independent risk factor for atherosclerosis and CVD, directed the research to find drugs which might decrease its levels in serum and therefore could prevent cardiovascular events in patients with elevated Lp(a) levels. Lp(a) is in fact an LDL cholesterol variant that contains an apolipoprotein(a) [apo(a)] [27]. Pelacarsen was one of the first drugs in class to be evaluated in humans and is currently in the most advanced phase of clinical trials [28]. It is an antisense oligonucleotide that binds to hepatocyte apo(a) mRNA and forms an ASO/mRNA complex that prevents the translation of apolipoprotein(a). This leads to decreased apolipoprotein(a) production and, by default, lower circulating Lp(a) levels [29]. Clinical trials of pelacarsen are still underway, but results published so far are rather optimistic, with phase II clinical trials already completed, and phase III currently in the recruitment stage.

Volanesorsen

Management of dyslipidaemia prior to the present day has mostly focused on LDL cholesterol. Currently, the focus is being switched to other particles such as triglycerides and triglycerides rich particles such as chylomicrons [30]. Chylomicrons are ultra-low-density lipoproteins that mostly contain triglycerides. An important protein found in chylomicrons is the apolipoprotein C-III. Numerous studies have demonstrated the importance of apoC-III in increasing circulatory triglyceride levels and intrinsic proatherogenic effects [29]. As such, apoC-III is a target for a new class of drugs aimed to lower triglyceride levels and indirectly preventing cardiovascular incidents and pancreatitis episodes in patients with hypertriglyceridemia. The first of these drugs is volanesorsen. It is an antisense oligonucleotide that binds to the ApoC-III mRNA and disrupts apoC-III translation. This leads to lower apoC-III levels and lower levels of chylomicrons and triglycerides [31]. Phase III clinical trial results for volanesorsen were published in 2021, with an observed reduction in triglyceride levels by 71.8% compared to the placebo group after a three-month period.

Olezarsen

Similar to volanesorsen, olezarsen is an antisense oligonucleotide targeting apoC-III, and through apoC-III translation disruption, chylomicrons and triglyceride levels are reduced. It is currently a next-generation antisense medicine in phase III clinical trials. The first results of the Phase II trial were published in early 2022. The treatment regimen tested was 10 mg every 4 weeks, 15 mg every 2 weeks, 10 mg every week, and 50 mg every 4 weeks. Olezarsen is administered subcutaneously. Evaluation was performed after 6 months of treatment with a reduction in triglycerides in patients receiving olezarsen treatment by 23%, 56%, 60%, and 60%, respectively. The safety profile seems to be the biggest benefit of olezarsen compared to volanesorsen, with no platelet count reduction and only mild injection site reactions as the main adverse effects observed [32].

Other Agents Approved by FDA

One of the first drugs developed for parenteral use in dyslipidaemia was mipomersen, an antisense oligonucleotide that targets apolipoprotein B (Apo B) mRNA and interferes with translation, thereby decreasing Apo B levels [33]. Apolipoprotein B is one of the main components of LDL and VLDL particles. The absence of Apo B decreases LDL cholesterol and total cholesterol levels in the blood. In studies, a 24.7% reduction in LDL cholesterol levels was observed over 26 weeks in patients receiving mipomersen compared to patients receiving a placebo. In 2012, the FDA approved mipomersen for subcutaneous administration at a dose of 200 mg once weekly in patients with homozygous familial hypercholesterolemia [34]. However, mipomersen had significant adverse effects ranging from local injection reactions to flu-like symptoms, causing many patients to discontinue treatment. The most serious adverse effect is liver toxicity, with an increase in liver enzymes and accumulation of liver fat [34][35][36]. Therefore, mipomersen was never approved by the EMA after two unsuccessful authorization attempts, and after initial approval by the FDA, mipomersen received a special hepatotoxicity warning and is available only in a restricted program.

Treatments in the Pipeline

Another substance currently in development targeting apo C-III, is an apo C-III short interfering RNA antagonist with the acronym ARO-APOC3 [37]. The preliminary results of a phase I trial evaluating the safety and key pharmacodynamics and lipid parameters in patients with severe hypertriglyceridemia, ARO-APOC3 caused a maximal mean reduction of 80% to 99% in apo C-III levels, and a maximal mean reduction of 74% to 92% in plasma triglyceride levels. Since an E3-ubiquitin ligase, an inducible degrader of LDL receptor (IDOL) can cause ubiquitination and degradation of LDL receptors in lysosome, potentially a novel regulator of LDL receptor expression, similar to PCSK9. Although there are so far no approved drugs for targeting the IDOL-LDL-receptor pathway, some recent studies have shown that IDOL might be a potential therapeutic target for treatment of hypercholesterolemia [38].

ANGPTL3 Inhibitors

One of the new possible targets for the treatment of dyslipidaemia is angiopoietin-like 3 protein (ANGPTL3), which is currently one of the main focal points of lipidology pharmaceutical studies. So far, different teams have attempted to target ANGPTL3 using different technologies such as monoclonal antibodies and antisense oligonucleotides. ANGPTL3 acts as an inhibitor of lipoprotein lipase (LPL) and endothelial lipase (EL) enzymes [39]. Both enzymes are important in the serum increase in triglycerides and LDL cholesterol, so inhibition of ANGPTL3 protein leads to the disinhibition of LPL and EL, and therefore a decrease in triglycerides and LDL cholesterol levels in circulation [40][41]. The first drug in the class of ANGPTL3 inhibitors is evinacumab, a monoclonal antibody already approved by the FDA and EMA for the treatment of familial hypercholesterolemia.

Lerodalcibep

Lerodalcibep inhibits PCSK9 by gene editing, using CRISPR-Cas9 techniques. It is a recombinant fusion protein of a PCSK9-binding domain (adnectin) and human serum albumin that increases its half-life to 12–15 days. This enables the administration in a small-volume injection only once a month [42]. A phase II study with this drug at a dose of 300 mg once a month in patients who had LDL cholesterol >2.0 mmol/L (~80 mg/dL) despite maximally tolerated statin treatment, decreased LDL cholesterol by more than 70% at the end of the 12-week study. The incidence of adverse events was almost equal to the one in the placebo group.

Vaccines against PCSK9

Another attractive strategy is based on vaccines against PCSK9, which should trigger the generation of host anti-PCSK9 antibodies and consequently neutralize PCSK9/LDL receptor interactions. A novel antiPCSK9 vaccine formulation, called liposomal immunogenic-fused PCSK9-tetanus peptide plus alum adjuvant (L-IFPTA), was recently designed. The efficacy of the L-IFPTA vaccine, containing two different epitopes belonging to PCSK9 and tetanus toxin proteins, has been observed in different animal models including mice and non-human primates [43]. For instance, it induced the production of

long-lasting functional and safe anti-PCSK9 specific antibodies in BALB/c mice and reduced LDL cholesterol and VLDL cholesterol levels by up to 51.7 and 19.2% in C57BL/6 mice, without any significant adverse events [44].

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