INHIBITORII PCSK9 – UN NOU MEDICAMENT CU EFECT DE REDUCERE A LIPIDELOR

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Rezumat

Hiperlipidemia este un factor de risc bine stabilit pentru dezvoltarea bolilor cardiovasculare. Prin prevenirea distrugerii receptorilor LDL, nivelurile de LDL-C pot fi reduse cu 50% -60% peste cele obținute numai prin terapia cu statine. PCSK9 este o proprotein-convertază, care este implicată în degradarea receptorilor de lipoproteine cu densitate mică (LDL) în ficat. Mutațiile din gena PCSK9 determină hipercolesterolemie familială la un subgrup de pacienți prin reducerea numărului de receptori LDL de pe suprafața hepatocitelor. În schimb, alte mutații PCSK9 au ca rezultat concentrații neobișnuit de scăzute ale colesterolului LDL plasmatic și un risc redus de boală aterosclerotică. Blocarea activității PCSK9 cu anticorpi monoclonali reduce degradarea receptorilor LDL și crește degajarea colesterolului LDL. Injectarea de anticorpi specifici PCSK9 suprimă concentrațiile de LDL-colesterol timp de câteva săptămâni.

Cuvinte-cheie: PCSK9 inhibitori, hipercolesterolemia.

Summary. PCSK9 inhibitors – a new drug of lipid lowering therapy

Hyperlipidemia is a well-established risk factor for developing cardiovascular disease. By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone. PCSK9 is a proprotein convertase which is involved in the degradation of low-density lipoprotein (LDL) receptors in the liver. Mutations in the PCSK9 gene cause familial hypercholesterolaemia in a subset of patients by reducing the number of LDL receptors on the surface of hepatocytes. Conversely, other PCSK9 mutations result in unusually low concentrations of plasma LDL cholesterol and a reduced risk of atherosclerotic disease. Blocking the activity of PCSK9 with monoclonal antibodies reduces the degradation of LDL receptors and increases the clearance of LDL cholesterol. An injection of PCSK9-specific antibody suppresses LDL-cholesterol concentrations for several weeks.

Key words : PCSK9 inhibitors,hypercholesterolaemia.

Резюме. Ингибиторы PCSK9 -новая лекарственная липидная терапия

Гиперлипидемия – это установленный фактор риска развития сердечно-сосудистых заболеваний. Путем предотвращения разрушения LDL-рецептора уровни LDL-C могут быть снижены на 50-60% выше, чем при терапии статинами. PCSK9 представляет собой пропротеин-конвертазу, которая участвует в деградации рецепторов липопротеинов низкой плотности (LDL) в печени. Мутации в гене PCSK9 вызывают семейную гиперхолестеринемию у пациентов, уменьшая количество рецепторов LDL на поверхности гепатоцитов. Напротив, другие мутации PCSK9 приводят к необычно низким концентрациям холестерина ЛПНП в плазме и снижению риска развития атеросклероза. Блокирование активности PCSK9 с моноклональными антителами снижает деградацию рецепторов LDL и увеличивает клиренс холестерина LDL. При инъекции PCSK9-специфического антитела подавляются концентрации LDL-холестерина в течение нескольких недель.

Ключевые слова: PCSK9 ингибиторы, гиперхолестеринемия.

Introduction

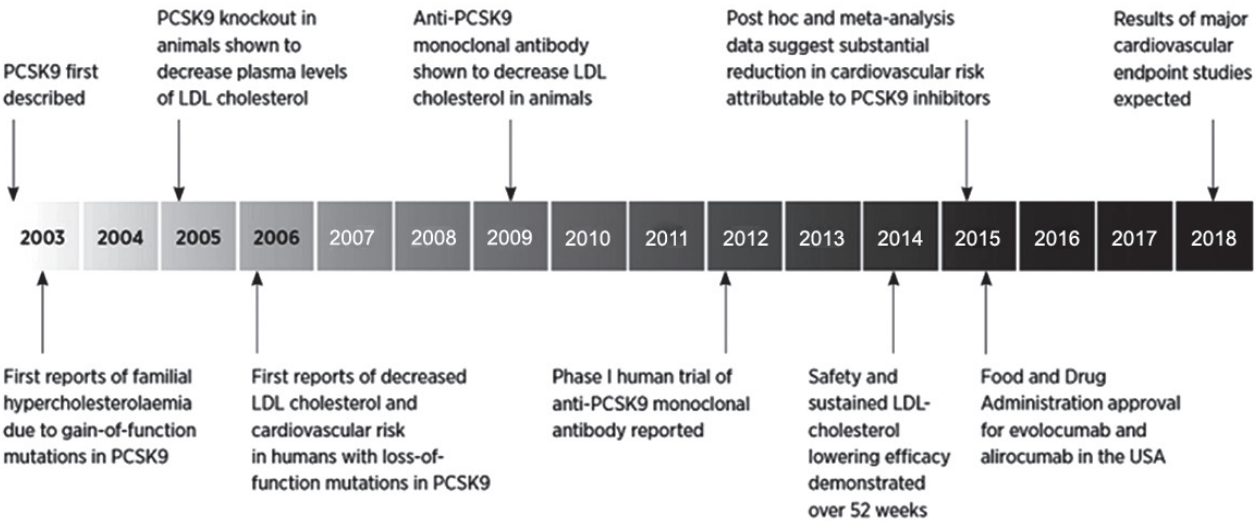
Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD)[1]. Multiple double blind placebo controlled trials have shown that treatment with HMG CoA Reductase inhibitors (statins) lowers low-density lipoprotein (LDL)-C levels and reduces CVD events in individuals with CVD or those at high risk for developing it [2, 3]. However, CVD events continue to occur in some patients on statins, despite receiving maximal tolerated therapy. Other patients develop side effects from statins that limit their use. Hence, newer modalities of treatment to lower LDL-C are needed in clinical practice. Recently the Food and Drug Administration (FDA) approved two medications which target a novel pathway to reduce LDL-C. They are monoclonal antibodies that inactivate proprotein convertasesubtilsin-kexin type 9 (PCSK9) [4]. The 1985 Nobel Prize for Physiology or Medicine was awarded to Michael Brown and Joseph Goldstein for their research into the link between cholesterol metabolism and coronary artery disease. This research increased our understanding of the pathophysiology of disorders such as familial hypercholesterolaemia, and paved the way for important therapies like statins

(HMG-CoA reductase inhibitors). They found that the low-density lipoprotein (LDL) receptor, expressed primarily in the liver, was responsible for clearing LDL particles from plasma. Statins decrease the intracellular concentration of cholesterol in the liver. This increases the expression of LDL receptors and more LDL cholesterol is removed from the circulation [5].

PCSK9 (proprotein convertase subtilisin/kexin type 9) was first described in 2003 (Figure 2). Hepatocytes are the predominant site for PCSK9 production, with other sites being intestines and kidneys [4]. PCSK9 reduces the number of LDLR in hepatocytes by promoting their metabolism and subsequent degradation [14]. PCSK9 has been shown to act both intracellulary (playing a role as a chaperone) as well as a secreted factor promoting LDLR internalization from the hepatocellular surface. Under normal circumstances, the LDL/LDLR complex is endocytosed by endosomes. In its active form, PCSK9 regulates cell surface receptors, in particular the LDL receptor. The enzyme encoded by the PCSK9 gene is primarily expressed in the liver [5].

PCSK9 inhibitory antibodies. Studies of uncommon mutations, such as the LDL-receptor mutations in familial hypercholesterolaemia, have led to important therapeutic advances in the study of lipids and cardiovascular disease. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme involved in the regulation of LDL receptors and LDL cholesterol. By tagging LDL receptors for destruction in the liver, PCSK9 increases concentrations of LDL cholesterol [6]. Plasma PCSK9 concentrations are raised by statins and this could attenuate the effect of these drugs. Research has focused on PCSK9 as a therapeutic target because blocking its action could reduce LDL cholesterol. The first candidates for therapies were humanised monoclonal antibodies. Alirocumab, evolocumab and bococizumab are in commercial development. These are all given by subcutaneous injection and reach a maximal effect 5 – 7 days after the dose, which lasts for about two weeks.Phase I trials started in 2012, and showed large reductions in LDL cholesterol. The antibodies were well tolerated, including in patients intolerant of statins. In addition to the effect on LDL cholesterol, PCSK9 inhibition also reduces lipoprotein(a) and has favourable effects on other lipoproteins such as triglycerides, HDL and Apo B [7]. Lipoprotein(a) is a recognised risk factor for atherosclerotic disease and, to date, has not been shown to respond to any conventional therapies.

Clinical studies. One of the first studies of PCSK9 antibody therapies was the RUTHERFORD study. This involved 167 very high-risk patients with heterozygous familial hypercholesterolaemia, treated with evolocumab every four weeks for 12 weeks. These patients were on stable lipid-lowering treatment with a statin with or without ezetemibe. The highest dose of evolocumab resulted in a drop in LDL cholesterol from 3,8 to 1,7 mmol/L (55%, $p<0.001$ vs placebo) [7]. The phase II OSLER-1 and phase III OSLER-2 studies were two open-label trials of evolocumab in combination with standard therapy. They involved more than 4000 patients for a median of 11,1 months. In patients treated with evolocumab, there was a fall in median LDL-cholesterol concentration from 3,1 mmol/L to 1,24 mmol/L (61%) with little change seen in the con-



LDL low-density lipoprotein

Fig. 1. Time-line of developments in the history of PCSK9.

trol group. Although the study design only allowed cardiovascular events to be analysed as an exploratory analysis, the event rate was 0,95% in the study group, compared with 2,18% in the control group (relative risk reduction 56%, p=0,003) [8]. The ODYSSEY phase III double-blind trial of alirocumab versus placebo involved 2341 patients at very high risk. Following injections every two weeks there was lowering of LDL cholesterol after 24 weeks. Major cardiovascular events were lower in the alirocumab group compared with controls (1,7% vs 3.3%, p=0,02). Lipoprotein(a) was also observed to fall by 26% [9]. Evolocumab is a human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9). Repatha binds to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, Repatha increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels [21]. *Repatha Cardiovascular Outcomes (FOURIER) Study: Key Outcomes.* The 27,564-patient Evolocumab cardiovascular outcomes study (FOURIER) demonstrated that adding Evolocumab to optimized statin therapy resulted in a statistically significant 20 percent (p<0,001) reduction in major adverse cardiovascular events (MACE) represented in the key secondary composite endpoint of time to first heart attack, stroke or cardiovascular death. The study found a statistically significant 15 percent reduction (p<0,001) in the risk of the primary composite endpoint, which included hospitalization for unstable angina, coronary revascularization, heart attack, stroke or cardiovascular death. The magnitude of risk reduction in both the primary and key secondary composite endpoints grew over time, with the robust benefit starting as early as six months and accruing through the median 2.2 years of the study. Patients on Evolocumab experienced a reduction in the risk of heart attack (27 percent, nominal p<0,001), stroke (21 percent, nominal p=0,01) and coronary revascularization (22 percent, nominal p<0,001) in patients treated with evolocumab and statin therapy compared to patients treated with placebo and statin therapy over a mean duration of 26 months. There was no observed effect on hospitalizations for unstable angina. Consistent with recent trials of more intensive LDL-C lowering, there was no significant effect on cardiovascular mortality [17-20].

Therapeutic use. To date, studies of anti-PCSK9 antibodies have examined the lowering of LDL cholesterol, with cardiovascular outcomes being analysed post hoc based on a relatively small number of events. Alirocumab and Evolocumab have recently been approved by the Food and Drug Administration (FDA). Much larger trials are in progress, which should determine cardiovascular outcomes and less common adverse effects. The FOURIER study of evolocumab involves 27 500 high-risk patients with cardiovascular disease on background statin therapy. Similar trials of alirocumab and bococizumab are in progress.Alirocumab was approved by the Food and Drug Administration in July 2015 for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolaemia or patients with clinical atherosclerotic cardiovascular disease. Alirocumab is available as a 75 mg/mL pre-filled pen or syringe and is given every two weeks by subcutaneous injection at a dose of 75–150 mg [10]. Shortly afterwards, evolocumab was approved for a similar group of patients. The recommended dose is 140 mg two-weekly or 420 mg once monthly. Evolocumab is available in a 140 mg/mL singleuse prefilled syringe or autoinjector [11]. The monthly dose of evolocumab is more than double the dose of two-weekly injections because the drug has non-linear pharmacokinetics. Its plasma concentrations do not increase in proportion to the administered dose [12]. Evolocumab was also approved in August, 2015 for use in adult patients with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic CVD requiring additional lowering of LDL cholesterol after being on a controlled diet and maximally-tolerated statin therapy [12, 13]. These new drugs for lowering LDL cholesterol may become a valuable addition to, or a substitute for, current lipid-lowering therapies. Until the results from large phase III trials are able to clearly delineate harms and benefits, their role is likely to be restricted to patients with a high cardiovascular risk who do not reach targets for LDL cholesterol with oral therapy. These trials may also uncover rare adverse effects. The need for subcutaneous injection may also make patients reluctant to use the antibodies, and some patients may need to have their doses administered by health professionals [14].

THOUSAND OAKS, Calif., May 16, 2018 / PRNewswire/ – Amgen (NASDAQ:AMGN) announced that the European Commission (EC) has approved a new indication in the evolocumab label for adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering low-density lipoprotein cholesterol (LDL-C) levels. With the expanded label now in place, Amgen is working with payers in Europe to remove prescribing barriers and expand access in order to reach patients

with established cardiovascular disease who are at risk of another event [15].

Adverse effects. Arthralgia, headache, limb pain and fatigue were more frequent in the OSLER studies of evolocumab than in controls, but liver function and creatine kinase were unchanged. Injection site reactions led to six patients (0,2%) stopping treatment. Neurocognitive changes were more common with evolocumab, but were infrequent (0,9%, compared with 0.3% in the placebo group) and were not related to the concentration of LDL cholesterol. A dedicated neurocognitive substudy of evolocumab is under way to give a more definitive assessment. The occurrence of adverse effects may have been confounded by the open-label method of the study, as patients treated with evolocumab were examined more frequently than controls. Evolocumab-binding antibodies were found in 0,3% of treatment and control patients, and were transient on repeat testing. No neutralising antibodies were observed.In the ODYSSEY trial overall adverse event rates were similar in the alirocumab and placebo groups. Discontinuation due to adverse events was 7,2% in the alirocumab group and 5,8% in the control group. Myalgia was more frequent with alirocumab than with placebo (5,4% vs 2,9%, p=0,006). Other adverse events included injection site reactions, neurocognitive events related mainly to memory, ophthalmologic events, and changes in transaminase and creatine kinase concentrations. The rate of diabetes development was not significantly different between groups [9, 16].

Conclusion

PCSK9 inhibitory antibody therapies target a novel pathway in LDL-cholesterol metabolism, and early phase I and II trials show highly promising result. The story of PCSK9 since its discovery just over a decade ago is an important case study in translating research into practice. PCSK9-inhibiting therapies have efficacy in lowering LDL cholesterol which could decrease the risk of atherosclerotic cardiovascular disease, particularly in high-risk patients. They could reduce the need for radical therapies such as lipoprotein apheresis in patients with severe heterozygous familial hypercholesterolaemia, and homozygous familial hypercholesterolaemia with residual LDL-receptor function.

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