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LEADING ARTICLE

Opportunities of new lipid-lowering therapy: proprotein convertase subtilisin/kexin type 9 inhibitors' clinical efficacy and safety profile

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Summary

Safe and evident reduction of LDL cholesterol in order to reduce the risk of cardiovascular complications is an important problem of modern cardiology. Results of new clinical placebo-controlled comparative studies investigating proprotein convertase subtilisin/kexin type 9 inhibition with monoclonal antibodies (mAb) indicate high potential of new group of drugs. This review article analyzes clinical efficacy and safety profile of alirocumab and evolocumab as a part of combined statin therapy.

Keywords

Lipid-lowering therapy, proprotein convertase subtilisin/kexin type 9 inhibitors.

Evolution of ideas about lipid-lowering therapy

Impaired lipid metabolism maintains the leading position between cardiovascular disease (CVD) risk factors [1]. The importance of this problem is determined by its high occurrence in population (according with epidemiological studies, up to 55% of adult Russian population) and inadequate control in patients with coronary heart disease (CHD).

In the population of high and very high risk of cardiovascular complications dyslipidemia is caused by several reasons: familial hypercholesterolemia, essential hypercholesterolemia, CHD, stroke, peripheral atherosclerosis, diabetes mellitus type 2, meta-

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bolic syndrome, chronic kidney disease, rheumatic and autoimmune diseases [2].

Nowadays the strategy of lipid-lowering therapy selection is actively discussed. Americal College of Cardiology/American Heart Association recommends combined therapy with two lipid-lowering drugs depending on the level of cardiovascular risk. European guidelines proceed with target therapy in order to achieve target lipid levels [3].

It is known that statins are widely used for hyperlipidemia treatment in different doses. In parallel the search of other effective lipid-lowering drugs is going on and it is determined by the necessity of more intense reduction of total cholesterol (TC) levels, restricted use of statins due to their adverse effects, bad tolerance or contraindications. Often combinations of two and more drugs are used to reach target lipid levels. ezetimibe and in some causes fenofibrate are used in clinical practice for this motivation [1].

Proprotein convertase subtilisin/kexin type 9(PCSK9) inhibitors: mechanism of action

For the first time the relation between PCSK9 and lipid metabolism abnormalities has been shown for patients with familial hypercholesterolemia [4]. In 2003 a new gene PCSK9 mutation of which led to familial hypercholesterolemia development has been identified. Later it has been shown that PCSK9 directly participates in low density lipid (LDL) receptors and apolipoprotein-E 2 type receptors degradation. PCSK9 is mainly expressed in liver, guts and kidney. PCSK9 mutations are linked with the development of both familial hypercholesterolemia (activating mutations) and familial hypobetalipoproteinemia (inactivating mutations). The correlation between PCSK9 plasma levels and TC, triglycerides, LDL cholesterol has been demonstrated in population studies for different ethnic groups. At the same time the correlation between PCSK9 and high density lipids has not been shown in any studies. Patients with familial hypercholesterolemia and PCSK9 gain-of-function(GOF) mutations have no strict correlation between PCSK9 plasma levels and mutation type. At the same time, there is significant correlation between PCSK9 plasma levels with mutation type not depending on LDL cholesterol levels in case of loss-of-function mutations (R46L, Y142X, C679X) that cause hypocholesterolemia [5].

During statins treatment PCSK9 levels increase that in its turn augments TC and LDL cholesterol levels [6]. Several studies demonstrated 14-47% increase of PCSK9 plasma concentrations depending on statins' type and dose. The mechanism of PCSK9 upregulation during statins treatment can be briefly explained like this. Statins administration leads to reduction of intracellular cholesterol levels. As a response to this, sterol regulatory element-binding proteins (SREBP) – transmembrane proteins of endoplasmic reticulum – are cleaved by serine protease 1 and transported by SCAP protein to the Golgi apparatus. Then SREBP undergo further processing by zink-metalloprotease (protease-2) that liberates regulatory domains of SREBP that are translocated into nucleus and consequently activate PCSK9 transcription.

Possible directions of PCSK9 inhibition include suppression of PCSK9 synthesis, blocking of PCSK9 and LDL cholesterol receptors interaction and increase of PCSK9 clearance. Monoclonal antibodies (mAb) are the drugs that currently undergo the investigation for inhibition of PCSK9 synthesis and PCSK9/LDL cholesterol receptor interaction and have successfully passed several stages of clinical trials [4]. Three PCSK9 inhibitors: alirocumab (REGN 727/SAR236553; Regeneron/ Sanofi), evolocumab (AMG-145, Amgen) and bococizumab (REGN 316 / PF-04950615; Pfizer) have reached the phase III of clinical studies and first two of them have been approved by Food and Drug Administration (FDA), two compounds: LGT209 (Novartis) an LY3015014 (Eli Lilly) are on the phase II of clinical trial. RG7652 (Roche/ Genetech) trial had been terminated in 2014.

Review of clinical studies investigating efficacy and safety profile of PCSK9 inhibitors

Creation of pharmacological agents lowering PCSK9 blood levels is one of important directions of lipidology. Use of these drugs in combination with statins seems to be promising because they can potentially increase hypolipidemic effects of statins.

Use of PCSK9 inhibitors, at first, had been considered for patients with familial hypercholesterolemia. The results of several multicenter randomized clinical trials of III phase had been published in 2015. Placebo-controlled trial RUTHERFORD-2 investigated 329 patients who received evolocumab in dose of 140 mg for 2 week or 420 mg per month during not less than 4 weeks during statins therapy [7]. LDL cholesterol levels reduced by 59% and 61% respectively after 12 weeks of therapy comparing with placebo. Target levels of LDL cholesterol have been reached in

more than 60% of cases. In the ODYSSEY FH II study high statin doses and their combination with other lipid-lowering drugs together with alirocumab administration in dose of 74/150 mg each 2 weeks comparing with placebo had led to LDL cholesterol levels reduction by 51-58% averagely after 24 weeks of treatment. Target levels of LDL cholesterol have been achieved in 60-68% of cases. Another study of ODYSSEY HIGH FH series investigated alirocumab efficacy in dose of 150 mg/2 weeks in 106 patients with LDL cholesterol concentration >4mmol/L that remained unchanged after high-dose therapy with statins and other lipid-lowering drugs. Target levels of LDL cholesterol have been reached in 57% of patients [8, 9].

The efficacy of PCSK9 inhibitors has been studied in parallel in patients with high cardiovascular risk during treatment with other lipid-lowering drugs and without them. The results of phase III clinical trials have been present in available literature.

The LAPLACE-2 study included 2067 patients with primary hypercholesterolemia or mixed dyslipidemia during moderate or intense therapy with statins. Patients of main group received evolocumab 140 mg/w weeks or 420 mg per month. In comparison group patients received ezetimibe 10 mg per day or placebo. After 10-12 weeks of observation LDL cholesterol levels reduction in the group of evolocumab therapy has reached 66-75% (140mg/2weeks) and 17-21% during ezetimibe treatment [10]. Another study DESCARTES investigated evolocumab 420mg/4 weeks efficacy in 901 patients with hyperlipidemia during diet with or without lipid-lowering therapy. After 52 weeks of observation the main group comparing with placebo demonstrated LDL cholesterol reduction by 56% during diet and by 62% during atorvastatin administration in 10 mg dose, by 57% - during atorvastatin 80mg, and by49% in the subgroup of atorvastatin 80mg/ezetimibe 10 mg combination.

Clinical efficacy of another PCSK9 inhibitor alirocumab in the dose of 75/150 mg each 2 weeks has been studied in the series of 7 trials with common name ODYSSEY (total number of patients was around 5000). Control groups were made of patients who received placebo or ezetimibe 10 mg per day. Basis therapy in main groups included statins (atorvastatin 20-40 mg per day or rosuvastatin 10–20 mg per day and also higher doses of statins) and in one study – ezetimibe, fenofibrate or diet. Average duration of study was 24 weeks. In the end of observation period LDL cholesterol concentration reduced by 32-68% comparing with placebo group [8, 9].

It is obvious that PCSK9 inhibitors administration additionally potentiates lipid-lowering effect of statins and in prospective it can be considered as a component of combined hypolipidemic therapy.

High attention is paid also to the monitoring of PCSK9 inhibitors safety profile since these drugs target intense reduction of LDL cholesterol levels.

International review articles often present detailed results of clinical studies dedicated to adverse effects of PCSK9 inhibitors. Systematized results about adverse effects are subdivided into several groups: total amount of adverse effects, reasons of therapy termination, severe adverse effects, reaction to injection and neurocognitive consequences [11]. These parameters have been included into clinical study protocols for evolocumab and alirocumab. It is necessary to point out that PCSK9 inhibitors safety has been studied in comparison with placebo or ezetimibe. In both groups statins were used in comparable doses and therapeutic regimens.

During alirocumab therapy with daily dose 75-150 mg and placebo or ezetimibe during 24 weeks any adverse reactions have been registered in 81 and 82,5% of cases and 71,2 and 67,2% of cases, respectively. It has been reported about early termination of therapy in all groups, average amount of registered cases has reached 8%: alirocumab against placebo (7,2% and 5,4%) or ezetimibe (7,5% and 5,4%), respectively. It is worth to notice that these differences were statistically insignificant. Severe adverse actions were described in the first groups in 18,7% and 19,5% of cases. Similar tendencies were observed during alirocumab and ezetimibe comparison: 18,8% and 17,8% of cases, respectively. Specific adverse reactions for example local reactions to subcutaneous injections were registered in 5,9% of alirocumab group cases versus 4,2% of placebo group cases, and in comparative study of alirocumab and ezetimibe these effects were described in 2,5% and 0,8% of cases, respectively. This study investigated also neurocognitive reactions that were registered in 1,2% and 0,5% , and also 0,8% and 1,2% of cases [12].

In clinical placebo-controlled trials investigating evolocumab in 420 mg during 52 weeks total amount of adverse effects was registered in the range of 31-60% of cases in the main group and 24-49% of cases in control group. Early termination of therapy due to adverse reactions was registered in 1-2% and 2-4% of cases respectively. Severe adverse reactions were registered in 0,9–2,7% of cases in evolocumab group and in 1,8–3,6% of cases in placebo group. Local ad-

verse reaction to subcutaneous injections was registered in 0% and 1,3% of cases respectively [13].

Thus, the review of international comparative placebo-controlled clinical trials demonstrated that LDL cholesterol levels reduction by PCSK9 inhibition with mAb is a promising therapeutic strategy due to significant clinical efficacy and good safety profile. Obviously that the spectrum of their use will be expanded from the treatment of familial hypercholesterolemia to indication in case of statins limitations and the necessity of evident lipid-lowering effect in order to reach target cholesterol levels. In future it is reasonable to perform series of clinical studies according with the endpoints and estimation of distant results of therapy.

Conflict of interest: None declared

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