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Reducing cholesterol levels to decrease cardiovascular events: the role of new proprotein convertase subtilisin/kexin type 9 inhibitors

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The need for new drugs to treat severe hypercholesterolemia is relevant because there are patients with genetic defects of cholesterol metabolism in whom current therapies are not effective enough or because there are patients at high risk for cardiovascular events necessitating extremely ambitious cholesterol targets and, finally, because in some patients the standard therapy is not well tolerated.

Even under optimal therapeutic conditions, maximal therapy with statin also in association with a second lipid-lowering agent (ezetimibe, ionic exchange resin, fibrates etc.) may not be sufficient to reach the therapeutic target. This situation is evident in patients with familial hypercholesterolemia the prevalence of which was initially estimated in 1/500 patients for the heterozygous form and 1/1000 000 for the homozygous form. More recent analyses, on a large population cohort, estimated the prevalence of the heterozygous form to be 1/200–300 and for the homozygous 1/300 000–400 000.[1] Another group of patients in whom the therapeutic target could be difficult to reach are those intolerant to statins. The prevalence of this condition is about 5–10%.[2]

For all those patients, new classes of drugs are being introduced that are able to act through different mechanisms of action than statins.

New cholesterol-lowering drugs

Four new classes of drugs designed to reduce LDL cholesterol (LDL-C) levels are currently in advanced phase of study. In patients with high or very high cardiovascular risk, those drugs are currently utilized in association with currently available lipid-lowering agents. For the inhibitors of the protein proprotein convertase subtilisin/kexin type 9 (PCSK9), studies testing efficacy with clinical cardiovascular endpoints are currently under way. Results of these trials should be available in 2–3 years.

(1) A first drug is the antisense oligonucleotide, mipomersen acting by decreasing the hepatic synthesis of apolipoprotein B (ApoB) through degradation of its mRNA with a reduction of assembly and production of all atherogenic lipoproteins. In heterozygote patients for familial hypercholesterolemia, cardiovascular disease and on maximal statin treatment, mipomersen decreased LDL-C by 28%, Lp(a) by 21% and ApoB by 26%.[3] Mipomersen has been approved only for treatment of patients with homozygous familial hypercholesterolemia by the Food and Drug Administration, because relevant side effects such as hepatic steatosis, inflammatory reactions at the site of injection and flu-like symptoms are commonly reported.

(2) Lomitapide inhibits microsomal triglyceride transfer protein (MTP) impairing hepatic production and secretion of Very Low Density Lipoproteins (VLDL), MTP is the key protein in the transfer of triglycerides on the apoprotein B. In patients with homozygous familial hypercholesterolemia being treated with diet only, the maximum reduction with lomitapide was of 51% for LDL-C, 79% for VLDL cholesterol, 65% for triglycerides, 56% for ApoB and 15% for Lp(a); unfortunately, hepatic steatosis was frequent as well as gastrointestinal side effects.

(3) The third class of drugs under investigation are the inhibitors of cholesterol ester transfer protein: anacetrapib reduces the exchange of cholesterol ester from HDL to ApoB lipoprotein (chilomicrons, VLDL and LDL), and the reverse transfer of triglycerides from ApoB-containing lipoproteins to HDL. Anacetrapib is the only drug in this class still under study; it can decrease LDL-C and Lp(a) by 40% if used in patients treated with statin and not affected by familial hypercholesterolemia, whereas it increases the HDL cholesterol by 140%.

(4) A new very promising class of cholesterol-lowering drugs are the monoclonal antibodies against PCSK9. PCSK9 significantly modulates the biologic cycle of the LDL receptors (LDLRs). This protein is synthesized and released by the hepatocytes (also by the intestine, the kidney and central nervous system), where it binds

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to the complex LDL–LDLR on the surface of the hepatocytes. Once bound to the LDL–LDLR complex and internalized in the hepatocytes, it prevents the intracellular recycling of the LDLR favoring its degradation and thus reducing the number of receptor on the cellular membrane. The monoclonal antibody interacting with PCSK9 prevents its binding to the LDL–LDLR complex favoring the recycling (rather than the degradation) of the latter on the surface of the hepatocytes. This mechanism allows more LDLRs on the cellular surface to be available to bind lipoproteins. The monoclonal antibodies anti-PCSK9 reduce LDL-C by 60–70% and Lp(a) by 20–25% in heterozygous patients for familial hypercholesterolemia treated with statins.[4]

Proprotein convertase subtilisin/kexin type 9 inhibitors

PCSK9 modulates LDL-C uptake by the liver. A 'gain-of-function' mutation of this protein is one of the genetic causes of autosomal dominant familial hypercholesterolemia. On the other hand, a 'loss-of-function' mutation is associated with low levels of LDL-C and reduction of coronary events without potential adverse effects on the general health. Several approaches have been suggested to inhibit PCSK9: inhibition of protein synthesis with antisense oligonucleotides or small RNA interfering with the protein synthesis, inhibition of the binding between PCSK9 and LDLR with mAbs, small peptides or adnectins and block of autocatalytic process of PCSK9 through small inhibiting molecules.[4,5]

Some monoclonal antibodies are in an advanced clinical testing phase, and they will become available for certain groups of patients in the fall of 2016. Alirocumab, Evolocumab and Bococizumab are those with ongoing phase 3 and clinical outcome trials.

Proprotein convertase subtilisin/kexin type 9 inhibitors for the treatment of familiar hypercholesterolemia

Patients with heterozygous familial hypercholesterolemia (HeFH) are in higher number than previously thought (1/200, in Italy 250–300 000 patients), underdiagnosed (only 4–5% of patients with HeFH are correctly diagnosed in Italy), undertreated (only one out 5–10 patients reaches target for LDL-C) and exposed to a high or very high cardiovascular risk.

The diagnosis of HeFH is based on simple criteria (Dutch Lipid Clinic Network criteria) and can be obtained in outpatients clinics; genetic assessment is necessary only when there is a high likelihood for familial hypercholesterolemia.[6] The lipid-lowering treatment with high-intensity statin therapy and ezetimibe should be implemented early on and ideally during adolescence.

The efficacy of monoclonal antibodies anti-PCSK9 in decreasing LDL-C in patients with HeFH on maximal lipid-lowering regimen has been evaluated in the ODYSSEY (alirocumab) and PROFICIO (evolocumab) programs.

For evolocumab, the RUTHEFORD[7] and RUTHERFORD-2[8] studies are available. RUTHEFORD-2 demonstrated that compared with placebo evolocumab (both single dose 420 mg subcutaneously once a month or 140 mg every 2 weeks) was well tolerated and after 12 weeks of treatment resulted in a further decrease of LDL-C by 60–65%; 70–80% of the patients reached the LDL-C less than 70 mg/dl target vs. only 2% of the patients on placebo (statin ± ezetimibe).

Alirocumab was tested in the ODYSSEY FH I and ODYSSEY FH II[9] studies and in the ODYSSEY HIGH FH in patients with severe HeFH. Compared with placebo, alirocumab (75 mg subcutaneously twice a month to 150 mg twice a month) was well tolerated and resulted in a further decrease in LDL-C by 50–55%; 72–80% of the patients treated reached the therapeutic target vs. 15% of the patients on placebo. In the ODYSSEY HIGH FH study, alirocumab 150 mg twice a month, in 107 patients with severe HeFH (baseline LDL-C > 160 mg/dl on maximal tolerated statin ± ezetimibe therapy) resulted in a further reduction of LDL-C levels of a mean 91 mg/dl (−50%) after 24 weeks; 57% of the patients reached a LDL-C target of less than 100 mg/dl and 32% a target of less than 70 mg/dl. Alirocumab was well tolerated in this study as well.

The monoclonal antibodies anti-PCSK9 are highly effective and with a good safety profile. These encouraging results were never achieved before in patients with HeFH.

Proprotein convertase subtilisin/kexin type 9 inhibitors for the treatment of patients with high cardiovascular risk

The ODYSSEY COMBO[10] evaluated 720 patients with high cardiovascular risk on maximal lipid-lowering treatment. The dose of alirocumab was the same as in the previous ODYSSEY studies. After 24 weeks, alirocumab further reduced LDL-C by 50.6% and after 50 weeks the effect was confirmed with an excellent compliance to the treatment.

LAPLACE-2[11] is a complex study in which patients receiving medium-to-high dose of statin were randomized to receive placebo or ezetimibe 10 mg or evolocumab at two different dosages: 140 mg every 2 weeks or 420 mg every 4 weeks. After 10 and 12 weeks, evolocumab reduced the LDL-C levels from 66% [95% confidence interval (CI): 58–73%] to 75% (95% CI: 65–84%) for the 140-mg dose and from 63% (95% CI: 54–71%) to 75% (95% CI: 67–83%) for the 420-mg dose.

Side effects were similar in all groups confirming the tolerability of evolocumab (most common side effects:

back pain, arthralgia, headache, muscular spasm and limb discomfort).

In a cumulative analysis of four phase II studies, evolocumab reduced Lp(a) by 29.5 and 24.5% after 12 weeks of treatment at the dose of 140 or 420 mg, respectively.[12]

In the ODYSSEY LONG TERM, safety, tolerability and efficacy of alirocumab vs. placebo were evaluated in high cardiovascular risk patients. In the ODYSSEY LONG TERM[13] study, alirocumab showed a promising efficacy profile with a good correlation between reduction of LDL-C and reduction of cardiovascular events. The post-hoc analysis demonstrated that the occurrence of adverse cardiovascular events (coronary death, nonfatal myocardial infarction, fatal and nonfatal stroke and unstable angina requiring hospital admission) was lower with alirocumab than with placebo (1.7 vs. 3.3%; hazard ratio 0.52; 95% CI: 0.31–0.90; $P < 0.01$).

The OSLER study,[14] including 1104 patients participating in different studies in which various doses of evolocumab were compared with placebo (MENDEL, LAPLACE-TIMI 57, GAUSS and RUTHERFORD), demonstrated a reduction of LDL-C levels by 58% after 1 year. The adverse events and severe adverse events were 69.2 and 7.5%, respectively, in the evolocumab group vs. 64.8 and 7.5% in the standard treatment group.

For patients with high cardiovascular risk and with high LDL-C level, there are new effective therapeutic options that re-emphasize the concept that 'the lower is better'.

The more promising new drugs according to their efficacy/safety profile are the inhibitors of PCSK9 that are based on a very solid pharmacological–biological rationale.

The therapeutic success accomplished with the addition of these drugs is not achievable with the current well tested treatment options.

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