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EDITORIAL

Inhibition of proprotein convertase subtilisin/kexin type 9 in the treatment of hypercholesterolemia☆

Inhibición de la proproteína convertasa subtilisina/kexina tipo 9 en el tratamiento de la hipercolesterolemia

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According to data from the World Health Organization, ischemic or atherosclerotic cardiovascular disease (ACVD) is the leading cause of death worldwide, especially in developed countries.[1] Atherosclerosis is a multifactorial artery disease in which deposition in the subendothelial space of lipoproteins transporting apolipoprotein B and cholesterol, mainly low density lipoproteins (LDL), and the subsequent inflammatory and proliferative events are essential for the development and clinical manifestations of ACVD. Atherosclerosis is therefore a ''cholesterol-dependent'' disease that starts with the deposition of cholesterol in the arterial intima.[2]

The main objective of strategies to prevent or treat ACVD is to decrease LDL cholesterol concentrations. Treatment with statins, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, which are able to lower LDL-C levels by 30–50%, has been shown to be beneficial for reducing cardiovascular disease, and is considered by all scientific bodies and guidelines to be the first treatment step because of its efficacy in lowering LDL-C and the risk of ACVD, with a greater than 21% reduction of major cardiovascular events per each 39 mg/dL decrease in LDL-C values. These results are independent of the baseline LDL-C value. Statins have a favorable safety and cost–effectiveness profile.[3] A combination of statins with other cholesterol-lowering drugs such as ezetimibe or resins enhances the reduction of plasma LDL-C levels and ACVD.

However, a significant proportion of patients cannot tolerate statins at the dose required to achieve control of LDL-C levels, and another subgroup, mainly consisting of patients with genetic hypercholesterolemia, shows partial resistance to statin action.[4]

New ways to lower LDL-C levels have therefore been investigated. The role of proprotein convertase subtilisin/kexin type 9 in cholesterol metabolism was recognized in two French families who were found to have the clinical phenotype of dominant autosomal familial hypercholesterolemia and mutations in the PCSK9 gene encoding protein PCSK9, not previously related to cholesterol metabolism. Interest in this PCSK9 protein started with this discovery and its being found to be a highly polymorphic gene.[5] Thus, gain-of-function mutations in the PCSK9 gene cause a new form of dominant autosomal hypercholesterolemia with a decrease in LDL receptors and, thus, a significant increase in LDL-C concentrations and high cardiovascular risk. On the other hand, subjects with loss-of-function mutations in the PCSK9 gene that increased the number of LDL receptors had decreases in plasma LDL-C levels and the risk of ACVD.[6]

Efforts therefore have focused on this new PCSK9 target involved in the cell metabolism of LDL. In plasma, PCSK9 binds to the LDL receptor (LDLR), and after the binding of circulating LDL to the membrane receptor bound to PCSK9, the LDL-LDLR complex internalizes into the cell and is transported to lysosomes, where cholesterol is released and LDLR is degraded when bound to PCSK9.[7] In the absence of PCSK9,

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the LDL receptor does not degrade in lysosomes after its internalization, and is transported again to the plasma membrane, where it binds to new LDL particles and internalizes them, so decreasing their plasma concentrations.

Various drug approaches have been proposed for inhibiting PCSK9 function in order to decrease plasma LDL-C levels and ACVD. Along this line, monoclonal antibodies that block PCSK9 in circulation have been developed; another line which has been investigated is based on the reduction of the hepatic synthesis of PCSK9 through micro-RNA or antisense oligonucleotides, and the third pathway proposed has been the inhibition of PCSK9 production in the hepatocyte.[8]

Anti-PCSK9 human monoclonal antibodies

There are currently at least three monoclonal antibodies that inhibit PCSK9 activity: evolocumab (AMG 145; Amgen), alirocumab (REGN727/SAR236553; Regeneron/Sanofi), and bococizumab (RN 316/PF-04950615; Pfizer). Other agents under development include: LGT209 (Novartis), RG7652 (Roche/Genentech), and LY3015014 (Eli Lilly).

PCSK9 inhibitors represent a new therapeutic class, and the use of anti-PCSK9 monoclonal antibodies in animal and human studies has been shown to be well tolerated after intravenous and subcutaneous administration, with an action lasting 2–4 weeks and a capacity to lower LDL-C levels by 60–70% as compared to placebo, with no significant effects on high density lipoprotein cholesterol and triglycerides, and an additional 65% reduction in subjects previously administered statins. They have also shown a low immunogenicity, and their main adverse effects are limited to injection site reactions and infusion reactions.[9]

The actions and effects of the administration of PCSK9-inhibiting monoclonal antibodies may be summarized using data from a recently published meta-analysis of 24 Phase 2–3 randomized studies with PCSK9 inhibitors compared to other types of treatment conducted on 10,159 patients with hypercholesterolemia. An additional 47.5% reduction in LDL-C, representing a statistically significant change (95% confidence interval [CI]: −69.6% to −25.4%), was found. Decreases were also seen in all-cause mortality (odds ratio [OR] of 0.45 [95% CI, 0.23–0.86]) and cardiovascular mortality (OR 0.49 [95% CI, 0.26–0.93]). Significant adverse effects did not increase after the administration of anti-PCSK9 antibodies, which are considered safe and effective in adults with dyslipidemia. The significant limitation of this meta-analysis is that the studies included were not designed to record events, and new studies currently ongoing should be awaited.[10]

As regards studies specifically designed to assess the capacity of PCSK9 inhibitors to decrease vascular events and to provide an evaluation of their long-term safety, special mention should be made of the FOURIER study, conducted on 27,500 subjects with established cardiovascular disease and comparing evolocumab and placebo[11]; the ODYSSEY OUTCOMES study of alirocumab, designed to study cardiovascular events in 18,000 subjects who had recently experienced an acute coronary syndrome[12]; and other studies with bococizumab (SPIRE 1 and 2) conducted on more than 18,000 patients.[13] All these studies will provide results on very long-term cardiovascular benefit and safety, but the first results will not be available until 2017 and 2018.

Anti-PCSK9 antibodies achieve significant reductions in total cholesterol, LDL-C, apolipoproten B, and lipoprotein (a) (Lp[a]). Decreases in plasma lipid levels are dose-dependent when these agents are used as monotherapy or combined with other lipid-lowering drugs. In different studies with evolocumab, where different biweekly and monthly subcutaneous doses were used, dose-dependent decreases in LDL-C levels ranged from 42% to 66% with biweekly treatment and from 42% to 50% with monthly treatment, with a significant Lp(a) decrease ranging from 18% to 32%. It should be noted that in the GAUSS study (NCT01375764), which consisted of 160 patients with statin intolerance, there were LDL-C reductions of 41–51% in patients who received evolocumab in monotherapy, of 63% in those given evolocumab plus ezetimibe, and of only 14% in those treated with ezetimibe alone. Adverse event rates were similar in all groups.[14]

PCSK9 inhibition associated with a maximum dose of highly potent statins may achieve LDL-C levels less than 25 mg/dL, but concern has been expressed with regard to long-term exposure to very low LDL-C levels because of the risk of complications such as hemorrhagic stroke, cancer, high blood pressure, impaired reproductive function, and neurocognitive dysfunction. In contrast to this line of thinking, healthy subjects homozygous for loss-of-function PCSK9 mutations have lifetime LDL-C levels ranging from 14 to 16 mg/dL and remain healthy in all aspects, including their cognitive and reproductive functions. This suggests that long-term inhibition with anti-PCSK9 antibodies is unlikely to have side effects.[15,16]

New potent and well tolerated cholesterol-lowering drugs are now available to complement the therapeutic options in subjects at high or very high cardiovascular risk, especially with genetic hypercholesterolemia, who do not achieve the proposed goals with standard treatment, statins and combinations with ezetimibe or resins, or in patients intolerant to statins who require reductions in LDL-C levels because of their high cardiovascular risk.

Conflicts of interest

The author has received fees for lectures and participation in scientific committees from Astra-Zeneca, MSD, Lilly, Novartis, Recordati, Esteve, Ferrer, Novonordisk, Danone, Praxis, Amgen, and Sanofi.

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