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EDITORIAL

New horizons in the treatment of hypercholesterolemia☆

Nuevos horizontes en el tratamiento de la hipercolesterolemia

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In recent years we have been experiencing great advances in the treatment of hypercholesterolemia, due to the appearance of new treatments with differentiated mechanisms of action and dosing regimens, which have demonstrated high efficacy and safety. The association of statins along with these new agents will enable us to achieve treatment objectives for LDL-cholesterol (LDL-C) in the vast majority of patients, including those with higher cardiovascular risk. However, it is necessary that physicians who are devoted to the prevention and treatment of cardiovascular diseases become familiar with these drugs in order to make rational use of them, in line with clinical practice guidelines. The aim of this monographic issue of *CLÍNICA E INVESTIGACIÓN EN ARTERIOSCLEROSIS* is precisely to describe the pharmacological basis and clinical pharmacology of these new drugs for the treatment of dyslipidaemias that have recently been marketed or that are in advanced stages of development.

In the first article, entitled "LDL cholesterol as a causal agent of atherosclerosis", Drs. Pedro-Botet, Benaiges and Climent summarise the most important data on the evolutionary development of LDL-C lowering drugs, cholesterol metabolism and the key role of LDL-C in atherosclerosis, referring to the evidence that supports the safety and preventive effect of clinical conditions that are accompanied by low LDL-C concentrations, for the treatment of cardiovascular disease. Regarding cholesterol metabolism, its biological role in humans, the regulation of its availability for cellular functions and its catabolism are all reviewed. The metabolism of lipoprotein particles, in particular LDL, and its role in the atherogenic process and in the appearance of atherothrombotic ischemic complications is also described, with special attention to the need for early and vigorous treatment of excess LDL-C to prevent the progressive accumulation of cholesterol in the arterial wall and undertake *aetiological treatment* of atherosclerosis. Similarly, the absence of negative effects of very low concentrations of LDL-C is confirmed, either for genetic or environmental reasons, and the causal effect of LDL, highlighting the effect of apoB-containing lipoproteins on cardiovascular risk. This is influenced by the scale and time of exposure to these particles.

In the second article in the monograph, entitled "The strict control of atherogenic cholesterol in the prevention of cardiovascular diseases" Dr. Carlos Guijarro reviews the main clinical trials on lipid-lowering treatment, mainly with statins, which have demonstrated the benefit and safety of lowering cholesterol to prevent cardiovascular diseases and

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set progressively more ambitious goals in the control of LDL-C. The next section, on intensive lipid-lowering combination therapy, describes trials with statins and ezetimibe, as well as with bempedoic acid, followed by a description of clinical trials with monoclonal antibodies against PCSK9; the Fourier study with evolocumab; and the Odyssey Outcomes study with alirocumab, which have demonstrated the efficacy and safety of extreme reductions in LDL-C with these agents. In the final section the importance of adherence to treatment and the cumulative effect over time are underlined, mentioning the role of new lipid-lowering treatments with a less demanding dosage, which can facilitate better adherence to intensive treatment, This is the case with inclisiran, a small interfering RNA (Pira) that offers sustained reductions in LDL-C around 55%, by means of half-yearly subcutaneous administration. Also covered is the positive effect of not delaying the initiation of intensive lipid-lowering therapy after a vascular event, achieving ambitious lipid targets as soon as possible and maintaining these in the long term.

The third article, by Dr. Luís Masana, entitled "New drugs to treat dyslipidaemia. From small molecules to small RNA interference" reviews the extensive evidence base for the benefit of lowering plasma concentrations of LDL-C on cardiovascular risk, and how this is the *primum movens* of lipid-lowering therapy. Likewise, this article describes the main treatment targets for this therapy. It includes a section on pharmacological action on triglyceride-rich particles, including those aimed at preventing VLDL synthesis, among which are mipomersen, lomitapide and n-3 fatty acids, and those aimed at increasing the plasma clearance of triglyceride-rich lipoproteins (TRLs), including evinacumab and volanesorsen. The inhibition of cholesterol ester transfer protein (CETP) by a new drug, obicetrapib, and the role of lipoprotein(a) as a clear therapeutic target are described below. The next section of the article, on new pharmacological mechanisms of action, includes classic small molecules, such as statins, ezetimibe or fibrates, and new drugs, such as bempedoic acid, muvalaplin, which inhibits lipoprotein(a), and lomitapide and obicetaprib, mentioned before. Monoclonal antibodies directed against PCSK9, alirocumab and evolocumab, are described in the following section to continue with an innovative mechanism, the blocking of protein synthesis by interfering in the translation of their messenger RNA by antisense oligonucleotides (ASOs) and PiRNA. Among the first described are AZD8233 (ION-863633), volanesorsen, mentioned earlier, olezarsen, vupanorsen and pelacarsen. PiRNAs include those directed against apo(a), olpasiran, zerlasiran, and lepodisiran, and those directed against ANGPTL3 (ARO-ANG3) and apo CIII (ARO-APOCIII). Within this section of small interfering RNA molecules, inclisiran is described more broadly; the first siRNA, approved for clinical use in the cardiovascular field and which targets the blockade of PCSK9 mRNA, inhibiting its synthesis. The molecular structure and main pharmacological characteristics of inclisiran are described here. Finally, and within the fight against the PCSK9 protein, new approaches currently under development are described, including vaccines, gene editing using CRISPR-Cas9 technology to silence the PCSK9 gene, macrocyclic peptides that inhibit the interaction of PCSK9 with the LDL receptor and adnectins, aimed at blocking the binding of PCSK9 to this latter receptor.

In the last article in the monograph, entitled "Efficacy, benefit and safety of inclisirán", Dr. López Miranda discusses the efficacy, benefit and safety of inclisiran. This article describes the extensive programme of clinical trials, known as the 'Orion programme', which studied the effects of this drug on lipid metabolism and its safety. The Orion programme included patients at high risk of atherosclerotic cardiovascular disease or with already established atherosclerotic cardiovascular disease (ACVD), and those affected by familial hypercholesterolemia (FH). Likewise, the results of real-life studies and clinical trials on cardiovascular prevention, currently underway, are also described, to then conclude with a detailed review of the safety of drugs in general, mentioning here that their side effects are similar to those of placebo. The article shows how inclisiran enables a decrease in high-intensity LDL-C that also extends to other atherogenic lipids, as well as in the PCSK9 protein, by means of basal subcutaneous administration, at 3 months and every 6 months thereafter, as a long-term maintenance regimen.

We hope that this monographic issue will enable you to become familiar with the new lipid-lowering drugs and that it meets the expectations of doctors who are dedicated to treating dyslipidaemia and, ultimately, to preventing cardiovascular diseases.