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EDITORIAL

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. A new drug class for the treatment of hypercholesterolemia☆

Inhibidores de proproteína convertasa subtilisina/kexina tipo 9 (iPCSK9). Los nuevos de la clase en el tratamiento de la hipercolesterolemia

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The new proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are LDL-cholesterol (LDLc) lowering drugs. The PCSK9i currently available on the market (alirocumab [Praluent®] and evolocumab [Repatha®]) are 100% human monoclonal antibodies that selectively bind in plasma to PCSK9, and prevent the latter from binding to the low-density lipoprotein (LDL) receptor. As a result, once this receptor has been internalized within the cell, bound to its ligand, it is recycled and returns to the membrane where it can continue to capture LDL.[1] The PCSK9i are the result of translational research in familial hypercholesterolemia (FH),[2] and the rapidity with which they have been marketed—barely 11–12 years after the identification of their therapeutic target (PCSK9) in the year 2003[2]—is quite remarkable. Equally surprising is the short time that was required for large preclinical trial programs (ODYSSEY in the case of alirocumab, and PROFICIO in the case of evolocumab) to be developed, in order to demonstrate their efficacy (mean LDLc reduction of 55–65%) and safety in different populations and clinical situations.[3]

The arrival of these drugs has been good news, especially for certain groups of patients. In this regard, first on the list of such groups are patients with FH, many of whom were not receiving sufficiently potent treatment. Now, in the absence of pharmacological intolerance, there is the possibility of reaching control targets in almost all patients with heterozygous forms of the disease (HeFH), thanks to the sequential combination of changes in lifestyle, high-potency statins ± ezetimibe, and PCSK9i.[4] Up to 60% of all patients with HeFH subjected to LDL apheresis could abandon this ultimate blood cholesterol-lowering treatment option, which is expensive for the system (minimum cost 15,000–20,000 euros/year) and inconvenient for the patient, due to the twice-weekly sessions and the need for vascular access.[5] The homozygous forms of FH will continue to require LDL apheresis to secure only partial control of the disease. Patients failing to reach the control targets in secondary prevention of cardiovascular disease may also benefit from PCSK9i. The residual risk in these patients is the subject of continuous analysis and debate. The LDLc concentrations clearly contribute to this risk,[6] and it was logical to presume that their reduction with PCSK9i would help reduce (though not eliminate) it. Treatment with evolocumab versus placebo, added to treatment with statins, mainly of

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high intensity and great multifactorial protective action, has been shown to reduce the mean relative cardiovascular risk by 15–20% (primary-secondary outcome) over two years of follow-up.[7] As expected, such protection increases after the first year of treatment and is independent of basal LDLc.[7] It is hoped that these findings will be confirmed in 2018 by a new study of events in a different high-risk population involving alirocumab.[8] Lastly, people requiring lipid-lowering treatment, particularly those belonging to the two above groups and who present statin intolerance, now have a treatment option for lowering their risk. In these individuals, PCSK9i have been shown to offer greater potency, with tolerance similar to that of the only comparator drug available to date in monotherapy, and which is sometimes used in such patients: ezetimibe.[9]

The studies involving PCSK9i (lipid-lowering efficacy,[3] reduction/absence of the progression of atherosclerosis,[10] and the reduction of clinical events),[7] the new unveiled physiology of LDLc homeostasis, and the results of studies in patients with genetic variants associated with a decrease in PCSK9 function[11] reaffirm LDLc as a causal factor of disease. Such studies, moreover, confirm that LDLc reduction as soon as possible in the natural course of atherosclerosis, and by any means,[7,12] reduces the risk of cardiovascular events. In this scenario we also must seek opportunities to identify the best candidates for treatment with PCSK9i.[13] The age of the patient, the benefits in terms of clinical events, absolute risk and initial LDLc values, and the expected absolute LDLc decrease—beyond the potent lipid-lowering effect of PCSK9i, or the question of whether the patient has failed to reach the control targets—must also be taken into account. It is increasingly necessary to evaluate the number needed to treat (NNT) in order to avoid an event and to conduct cost/benefit analyses allowing us to identify and to continue to characterize the best candidates (by adding factors such as diabetes, family history, and LPA level). It is clear that such analysis should not be limited to the short term, since patient risk is not established in the short term. The undeniable clinical benefits afforded by evolocumab even in patients with a mean LDLc concentration of 73 mg/dl,[7] cannot be directly transferred to clinical practice, at least not at its current price. We would have to treat 74 of these patients (a ''mean FOURIER patient'' in secondary prevention with mean LDLc 92 mg/dl) for two years in order to prevent one cardiovascular event.[7] While waiting for these analyses, the scientific bodies concerned have adopted positions with regard to the risk profile and minimum required LDLc level (>100 mg/dl),[14] and the national health authorities,[15] as well as the authorities of some of the Autonomous Communities,[16] have declared themselves willing to cover the associated public costs.

In general, PCSK9i have caused us to further reflect upon the cost of cardiovascular prevention, one of the factors being the money we spend on drugs. Undoubtedly, such prevention would be improved with the adoption of primary prevention health policies and other proactive strategies that are economically feasible, while taking into account the cost of the new drugs in the context of cardiovascular prevention. It is essential to find opportunities for improving the balance between sustainable public and population-based healthcare and the new more personalized care in relation to necessary cardiovascular prevention, at a time when it is rare to find at least ''good'' cardiovascular health.[17] In this field, such opportunities could include:

1. Improvements with regard to the systematic underdiagnosis of patients with FH, a disease in which the first event is preventable if it is identified early enough.[18] Following the first cardiovascular event, which in these patients occurs 10–20 years earlier than in the general population, most, if not all, of the patients will need PCSK9i in order to reach the new control targets of LDLc < 70 mg/dl, or at least <100 mg/dl. If treatment is limited to statins, 40% of these individuals will probably suffer another major cardiovascular event.[19]
2. A general improvement of secondary prevention in cardiovascular disease, as the situation with the greatest known cardiovascular risk in clinical practice, by means of a multifactorial intervention. Less than 50% of all Spanish patients in secondary prevention have at least LDLc < 100 mg/dl, with the inadequate potency of the treatments theoretically available before the introduction of PCSK9i being one of the determining factors.
3. An improvement in adherence to the current treatments (statins and/or ezetimibe) in those patients that really need them. It has been estimated that 20% of all patients stop taking statins[20] because of suspected side effects (without due confirmation in most cases), resulting in a rise in cholesterol and the possible triggering of cardiovascular events.[21] Consultation concerning the indication, shared decision making, emphasis on the need to maintain the treatment, confidence in the health professional (and his or her ongoing training), and therapeutic education are key elements for improving patient adherence to drug treatment. In this regard, PCSK9i are not simply another treatment alternative but predominantly constitute the final therapeutic step. Before prescribing PCSK9i, it is necessary to assess patient adherence to statins, which are potent and safe drugs, with an excellent risk/benefit ratio, and which have been used for over 20 years in many different types of patients.[22]

Lastly, PCSK9i monoclonal antibodies are drugs prescribed on a chronic basis, in people with serious diseases, and are used to avoid disease progression and improve quality of life. The potential short- and long-term side effects, interactions with other drugs, the form of treatment and dosing regimen, and the credit or discredit of the prescribed drugs are all crucial issues for patients today, who receive (and act upon) information not only from health professionals, but also from other sources. The PCSK9i safety profile observed to date (2–4 years of continuous treatment in thousands of patients), under controlled clinical trial conditions, has been positive in terms of both adverse effects and the probability of reaching and maintaining mean LDLc concentrations of 25–40 mg/dl.[23,24] Recently, at the 2017 congress of the American Heart Association (the EBBINGHAUS study), it was reported that no evidence had been found that evolocumab and/or the mean LDLc concentration of 30 mg/dl reached by using the drug were associated with patient cognitive disorders during the intervention period.[25] Needless to say, in the same way as with other drugs, partic-

ularly those administered on a chronic basis, it is essential to continue evaluating the safety profile by means of post-marketing pharmacovigilance campaigns.

In conclusion, the introduction of the new PCSK9i has been positive for patients with diseases associated with a very high cardiovascular risk, since in the context of a multidisciplinary strategy, these drugs can contribute to lowering the risk and preventing a worsening of patient quality of life. This is the available evidence on which their use is based today. On the other hand, PCSK9i should also serve as both an alert and an opportunity for the public health system. They constitute an alert because of the high cost of the new drugs being developed for cardiovascular prevention purposes, due to the technology invested in their development and the large number of patients theoretically able to benefit from their use. These drugs likewise constitute an opportunity for launching or consolidating clinical initiatives and healthcare policies aimed at better identifying patients at risk (also in the primary prevention setting) and at preventing cardiovascular events due to the adoption of simpler, inexpensive and (as far as possible) personalized management strategies. This would help us to avoid increasingly costly treatments that the public health system has difficulty in maintaining.

Conflicts of interest

Emilio Ortega has participated as principal investigator in research projects sponsored by Amgen, Sanofi and Pfizer. He has received payment for consultant activities and/or speeches from Sanofi, MSD and Amgen.

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