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Editorial

PCSK9 Inhibitors: From Innovation to Sustainable Clinical Application

Los inhibidores de PCSK9, de la innovación a la aplicación clínica sostenible

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INNOVATION, CLINICAL APPLICATION, AND SUSTAINABILITY IN THE PUBLIC HEALTH SYSTEM

Proprotein convertase subtilisin/kexane 9 (PCSK9) inhibitors represent a therapeutic innovation in the treatment of diseases linked to excess plasma cholesterol and are revolutionizing the understanding of cholesterol metabolism.[1]

PCSK9 inhibitors are monoclonal antibodies that bind to PCSK9, an important metabolic regulator of low-density lipoproteins (LDL), and help stop the breakdown of LDL receptors, thus increasing their expression. This allows plasma LDL-C concentrations to be reduced by up to 60% when PCSK9 inhibitors are used with high-intensity statins, and reduces cardiovascular morbidity and mortality by around 20% at 2 years of treatment.

Following several studies in patients with familial hypercholesterolemia (FH), PCSK9 inhibitors have been studied as secondary prevention, specifically in patients with high residual risk and in those not tolerating statins. Their efficacy and safety in this context have been demonstrated in the FOURIER trial with evolocumab[2] and the ODYSSEY Outcomes trial with alirocumab (the latter is pending publication, but was presented at ACC 2018; NCT01663402). Both trials, which include cardiovascular morbidity and mortality outcomes for close to 50 000 patients in total, have shown significant clinical benefit in terms of cardiovascular events. Furthermore, in the ODYSSEY Outcomes trial, a significant additional benefit in all-cause mortality was recorded, as well as a trend toward reduced cardiovascular mortality.

Both evolocumab and alirocumab were approved in record time by the European Medicines Agency and the Food and Drug Administration, after demonstration of the efficacy, safety, and protective cardiovascular effect of these monoclonal antibodies. From the first studies on the role of the protein to marketing the drug took just 10 years. The main problem facing the use of these drugs in clinical practice is their high cost, so the different health care systems only fund them under certain conditions and if supported and recommended by the various scientific societies.

In Spain, the therapeutic positioning report by the Ministry of Health, Social Issues and Equality and the Spanish Agency of Medicines and Medical Devices[3,4] is generally taken to be the main document used by the various autonomous communities when funding these drugs, with some differential arrangements. Based on the criteria within this and other documents, estimation of the number of patients who would be candidates for treatment, particularly with more costly drugs, is of unquestionable relevance to establish the impact on a country's health care spending.

In a recently-published article in *Revista Española de Cardiología*, Zamora et al.[5] report an interesting study in which they aimed to estimate the number of patients who would be candidates for PCSK9 inhibitors in real-life clinical practice, analyzing the data from 2.5 million participants from the Spanish population older than 18 years. The use of an accredited database, such as the Information System for the Development of Research in Primary Care (SIDIAP)[6] of the Catalan Health Institute, the size of the sample, and the availability of data from clinical practice were amongst the strengths of this contribution. The authors of the study mention some of its limitations, but the conclusions are sound. Zamora et al.[5] estimate the number of over-18s eligible for PCSK9 inhibitors in conditions of everyday clinical practice to be very high, ranging from 0.1% to 1.7%, depending on the criteria used in the recommendations of the various scientific societies, in this case the Spanish Society of Cardiology, the Spanish Society of Arteriosclerosis, the European Society of Cardiology/European Atherosclerosis Society, and the National Institute for Health and Care Excellence guidelines. These large differences are explained by the LDL-C figure stipulated by each society and for each risk group, which are not always the same. The study does not analyze the subgroup of patients who are intolerant of statins, given the complexity of such an analysis and the lack of reliable data.

This study also highlights the need for optimal treatment in at-risk patients, regarding both lifestyle measures and drug therapy (high-intensity statins and ezetimibe to reduce LDL-C by at least 50%), and for medication adherence of over 80%. Information technology systems in the various autonomous communities, via electronic records, can be used to check these highly important targets.

As physicians, we must consider the patient as a whole, taking into account his/her risk profile, to be able to make the best decisions regarding treatment. The benefits of treatment will depend on the risk level multiplied by the risk reduction associated with the drug. Furthermore, it is well-known that multiple factors besides LDL-C affect the likelihood of subsequent events. Among them are age, control of blood pressure and diabetes, and the extent of not only coronary vessel disease but also the involvement of multiple vascular territories. Consequently, patients with higher risk may obtain large reductions in absolute risk, but even patients with lower LDL-C levels may also benefit. To give an example of the need for a holistic approach to residual risk, in the landmark intervention studies on PCSK9 inhibitors (FOURIER and ODYSSEY Outcomes) it was reported that 28% and 24% of patients with atherosclerotic cardiovascular disease were active smokers. Therefore, addressing this well-known harmful risk factor is essential.

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Given the volume of patients who are potential candidates for treatment with PCSK9 inhibitors, it is essential to have a well-defined profile of those who would benefit most. Even in groups at higher risk—such as patients with FH in its various forms, those in secondary cardiovascular disease prevention, or intolerant to statins—it is important to determine with appropriate studies if these drugs would be cost-effective.

ARE THERE ANY DATA TO IDENTIFY PATIENTS AT VERY HIGH RISK WHO WOULD BENEFIT MOST FROM TREATMENT?

Patients with FH have up to 4 times the risk of a cardiovascular event than those without FH. The investigators involved in the SAFEHEART registry developed the first equation that can help predict risk of cardiovascular events in FH, based on easy-to-obtain clinical predictors.[7] Age, male sex, a past history of cardiovascular disease, body mass index, active smoking, and plasma LDL-C and lipoprotein(a) concentrations were independent predictors of cardiovascular events. This prospective registry did not include some of the expected risk factors because they did not improve accuracy in the final predictive model. The LDL-C level reached is more important than the drug used in treating FH.[8,9] The presence of diabetes was not predictive of cardiovascular events, probably because of its low prevalence; nor was the type of mutation selected in the model, which again implies that to predict outcomes, LDL-C levels are more important than the type of molecular defect. This reinforces the concept that phenotype is more important than genotype in patients with FH.

In an analysis of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), the investigators tested the hypothesis that stratification of atherothrombotic risk could be useful to identify patients at higher risk after acute coronary syndrome.[10] They used the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention, a simple instrument with 9 clinical parameters (heart failure, hypertension, age $>$ 75 years, diabetes mellitus, previous stroke, previous coronary artery bypass surgery, peripheral arterial disease, glomerular filtration rate $<$ 60 mL/min, and active smoking). They hypothesized that the identification of patients at increased risk and treatment of this subgroup would lead to the greatest benefit. Awarding 1 point to each variable, they identified patients as low-risk (0-1 point), intermediate-risk (2 points) or high-risk ($\geq$ 3 points).

A substudy of the FOURIER trial looked at 22 351 patients with a previous myocardial infarction, characterizing them according to time since the most recent infarct, number of prior infarcts, and the presence of residual multivessel disease (stenosis $\geq$ 40% in at least 2 vessels).[11] Analyzing the absolute and relative reduction in events included in the primary and secondary outcomes of the trial in these subgroups, the authors concluded that patients with more recent infarcts, multiple previous infarcts, and residual multivessel disease had a higher risk of major cardiovascular events and had the greatest reductions in LDL-C with evolocumab. In the FOURIER trial, patients with peripheral arterial disease[12]—who are at high risk of cardiovascular events—and who were treated with evolocumab had the greatest reductions in absolute risk of complications (acute ischemia, major amputation or urgent peripheral revascularization due to limb ischemia).

The inflammatory aspect[13] of residual risk after treatment with high-intensity statins has been classified into several categories: patients with high residual lipid risk with LDL-C $\geq$ 70 mg/dL despite treatment, those with residual inflammatory risk with high-sensitivity C reactive protein (hsCRP) $\geq$ 2 mg/L, those who meet both conditions, and those who meet neither. Both the PROVE-IT (pravastatin 40 mg vs atorvastatin 80 mg) and the IMPROVE-IT (simvastatin vs ezetimibe) trials demonstrated that around 50% of patients had residual inflammatory risk and that, even when LDL-C was reduced to 50 mg/dL, half of those treated still had hsCRP $\geq$ 2 mg/L.[14]

It is not yet known if the efficacy of PCSK9 inhibitors is influenced by patients' baseline inflammatory risk. Another FOURIER substudy[15] demonstrated that the reduction in LDL-C levels with evolocumab added to statins reduced cardiovascular events to a greater extent in patients with higher hsCRP levels. Event rates were lowest in patients with lower levels of hsCRP and LDL-C.

As we await the publication of the ODYSSEY Outcomes trial results and data analysis, it seems that more effort must be made to apply risk scoring that, using simple, easy-to-obtain clinical parameters, including some of those mentioned here, with or without biomarkers, allows us to identify patients who are candidates for PCSK9 inhibitors. There are 3 fundamental factors: baseline LDL-C concentration, the patient's absolute risk, and the relative risk reduction obtained with treatment.

CAN—OR MUST—PCSK9 INHIBITORS BE COST-EFFECTIVE?

The literature on the cost-effectiveness of PCSK9 inhibitors is vastly heterogeneous. The various studies use Markov models and run different simulations with varying prices and imputing different costs to the events, in distinct types of patients. Essentially, though, they are patients with FH, patients in secondary prevention following myocardial infarct or stroke, and patients with polyvascular disease and diabetes, and the results are expressed as QALY (quality of life years gained) and ICER (incremental cost-effectiveness ratio). In studies in the United States, given the initial cost of PCSK9 inhibitors there, cost-effectiveness studies have been negative in all scenarios, and uncertain in FH. Some studies do conclude that it is absolutely essential that adherence be improved. In fact, in a study by Virani et al.[16] it was noted that approximately a quarter of United States veterans aged between 40 and 85 years with atherosclerotic cardiovascular disease would be candidates for evolocumab according to the FOURIER criteria. In this context, the use of high-intensity statins combined with ezetimibe could reduce the need for evolocumab by 60%. It was also noted that, for these drugs to be cost-effective, their cost would need to be reduced by around 70%.

European studies have been similar, but with different simulations. One study conducted in Norway[17] considered PCSK9 inhibitors cost-effective only in an older, very high-risk population. In contrast, a recent Dutch study[18] looked at the cost-effectiveness of PCSK9 inhibitors added to standard lipid-lowering therapy in patients with high risk of vascular disease, with FH, vascular disease with high risk of recurrence, and patients with vascular disease with and without diabetes, using a model that calculated the ICERs for PCSK9 inhibitors for different treatment effects, assuming different costs, from €6000 to €3000. The results of this study may be useful in decision-making for those involved in funding.

Two cost-effectiveness studies in the Spanish population have been published, with disparate results.[19,20] The first study, on evolocumab in patients with high risk (FH and baseline LDL-C $>$100 mg/dL) or patients in secondary prevention, concluded that evolocumab treatment added to standard treatment could be a cost-effective option.[19] The other study, recently published in *Revista Española de Cardiología*, concluded that, although there were some important limitations, evolocumab was associated with a lower frequency of cardiovascular events, but that it would be inefficient for patients eligible to receive it via the National Health System.[20] Given the heterogeneity of the studies and the notable decrease in the price of the drugs, further cost-

effectiveness studies will be needed, based on detailed analysis of the FOURIER and ODYSSEY Outcomes trials with correct cost imputation and a life-long timeline. The aim should be optimal medical treatment with regards lifestyle, use of high-intensity statins and ezetimibe, as well as control of other risk factors, including educational measures and encouragement of treatment adherence. The EUROASPIRE V registry, presented at the May 2018 European Atherosclerosis Society congress, which includes the findings from 8261 patients in secondary prevention (median age, 64 years, 26% women) from 131 centers in 27 European countries, indicated that much remains to be done for the European lipid guidelines to be fully implemented. While most patients receive lipid-lowering therapy (84%), only 1 in 3 (32%) reach LDL-C levels < 70 mg/dL, probably due to the continued low rate of use of high-intensity statins (43%) after hospital discharge. In Spain, where 8 hospitals with and without cardiac rehabilitation units participated, the LDL-C target was met in 50%.

Finally, we must move toward risk weighting systems that can better stratify risk within each patient subgroup to identify who is likely to derive the greatest clinical benefit. A services portfolio that satisfies scientific cost-effectiveness criteria is an important cornerstone for the sustainability of the public health system and the healthcare component of the welfare state, to which all physicians must be committed.

CONFLICTS OF INTEREST

None declared.

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