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Experience with PCSK9 inhibitors from a Nephrology unit

Experiencia con inhibidores pcsk9 desde una consulta de nefrología

Dear Editor,

There is clear evidence about the role of low-density lipoproteins (LDL) in the process of atherosclerosis. Chronic kidney disease (CKD) entails high/very high cardiovascular risk (CVR) associated with multiple classic and non-classic CVR factors related to CKD. Despite the evidence for the benefit of lowering LDL cholesterol (LDL-C), the percentage of the population achieving guideline-recommended goals, including in CKD, remains low.[1] In recent years, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have been shown to reduce the risk of cardiovascular disease (CVD) when added to statin therapy by potently lowering LDL-C levels.[2]

The aim of this retrospective observational study was to evaluate the profile of patients who started treatment with PCSK9i (alirocumab or evolocumab), added to their usual lipid-lowering treatment, when they did not meet the recommended LDL-C goal according to their CVR, from a Nephrology unit, and the lab test changes achieved with this treatment.[3] The LDL-C goal in high CVR was <70 mg/dl and in very high CVR < 55 mg/dl. The Hospital Dr. Peset ethics committee approved the study.

We define high-intensity lipid-lowering therapy (HILLT)[4] as high-intensity statins alone (atorvastatin 40–80 mg, rosuvastatin 20 mg) or medium-intensity statins (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, pitavastatin 2–4 mg) combined with ezetimibe. We define atherogenic dyslipidaemia (DL) as triglycerides (TG) >150 mg/dl, together with HDL cholesterol (HDL-C) <40 mg/dl in men or <45 mg/dl in women.

In total, 43 patients were analysed, with a median follow-up of 12 (7–19) months: mean age 65 ± 12 years, 58.1% of the series were male. 65.1% had CKD and there were five kidney transplant patients (11.6%). 79.1% had a history of CVD. There were 13 statin-intolerant patients (30.2%); 69.8% were on statins and 34.9% on ezetimibe (32.6% of the series on statin-ezetimibe combination); 58.1% of the series were taking HILLT. The baseline clinical characteristics of these patients are shown in Table 1. In 79.1% of cases the first PCSK9i prescribed was evolocumab. Only three patients (7.1%) had to discontinue the drug due to intolerance.

Table 2 shows the lab test results before and after starting PCSK9i. The LDL-C before starting PCSK9i was 120 mg/dl (102–154). Treatment with PCSK9i led to significant reductions in total cholesterol (TC), LDL-C and TG, with LDL-C being reduced by 61%. This allowed 59% of the patients to achieve their recommended LDL-C goal. A significant difference in LDL-C reduction achieved with PCSK9i was seen between patients that were previously with or without statins, with a greater reduction in those on statins (66% vs 48%). No signifi-

Table 1 – Baseline characteristics of the series.

	n (%)
CKD (GFR < 60 ml/min/1.73 m^2)	28 (65.1)
GFR <30 ml/min/1.73 m^2	10 (23.3)
Albuminuria (uACR >30 mg/g creatinine)	26 (60.5)
HT	40 (93)
DM	9 (20.9)
Pre-diabetes/abnormal basal glucose	18 (41.9)
Atherogenic DL	8 (18.6)
CVD	34 (79.1)
Peripheral arterial disease	18 (41.9)
Coronary heart disease	15 (34.9)
Stroke	11 (25.6)
Heart failure	8 (18.6)
Asymptomatic plaques	2 (4.7)

CKD: chronic kidney disease; CVD: cardiovascular disease; DL: dyslipidaemia; DM: diabetes mellitus; GFR: glomerular filtration rate; HT: hypertension; uACR: urine albumin-creatinine ratio.

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Table 2 – Lab test results before and after treatment with PCSK9i.

	Before	After	p	%change
TC (mg/dl), median (IQR)	198 (175–257)	122 (100.25–165)	0.000	−38
LDL-C (mg/dl), median (IQR)	120 (102.25–154)	43 (23–82)	0.000	−61
HDL-C (mg/dl), median (IQR)	48 (43–56)	51 (41–62.25)	0.537	+3
TG (mg/dl), median (IQR)	145 (98–183)	113.5 (83–152.5)	0.003	−17
Creatinine (mg/dl), mean ± SD	1.62 ± 0.87	1.79 ± 1.29	0.149	NP
GFR (ml/min/1.73 m^2, mean ± SD	52.88 ± 30.04	51.83 ± 28.84	0.839	NP
uACR (mg/g creatinine), median (IQR)	49 (10–588)	31.5 (10–567)	0.407	NP

GFR, glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; NP: not performed; SD: standard deviation; TC: total cholesterol; TG: triglycerides; uACR: urine albumin-creatinine ratio.

cant differences were found in renal function or albuminuria levels.

This study found a significant reduction in LDL-C, similar to that reported in clinical trials with these drugs, including the renal patients.[2,5,6] This has enabled a large percentage of high/very high CVR patients to achieved their LDL-C levels that previously had failed to do so with conventional therapy. Similar real-life studies have been published here in Spain, with comparable results. The RETOSS-NEFRO[7] and RETOSS-CARDIO[8] studies share the experience of Spanish Cardiology and Nephrology units with evolocumab. The LDL-C reduction in both studies was around 60%, similar to our results. In another study concerning experience in a tertiary hospital,[9] reductions of around 55% were achieved. These studies have also shown very good tolerance to the drug, with low discontinuation rates.

Our study analysed the reduction in LDL-C according to whether or not the patient was previously on statins, and found better results in those patients taking a statin. This may show the synergistic effect on metabolic pathways of combination therapies.[4]

Although this study did not analyse other lipid parameters not commonly used in clinical practice, PCSK9i have been shown to reduce lipoprotein-a — and other atherogenic molecules, and to have an impact on the concentration and size of lipoparticles. This is of particular interest in renal patients, since classic oral lipid-lowering therapy has not shown much benefit in advanced CKD, and one of the reasons could be the lack of efficacy of statins and ezetimibe on lipid parameters not routinely measured or the size of lipoparticles, with these being particularly abnormal in the renal population.[10] Given the benefit seen with evolocumab in different stages of CKD,[5] future studies are warranted to analyse the impact of PCSK9i on all these lipid parameters and their prognostic impact, especially in the renal population.

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Conflicts of interest

V. Escudero has received lecture fees from Sanofi and Amgen. C. Castro has received lecture fees from Amgen. The other authors have no conflicts of interest to declare.

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Acute kidney injury (AKI): Spanish nomenclature also matters here

AKI (*Acute Kidney Injury*): AQUÍ la nomenclatura también es importante

Dear Editor,

We recently led a multinational initiative to standardise our nephrology nomenclature in Spanish,[1] following the Kidney Disease Initiative Global Outcomes (KDIGO) Consensus Conference on Kidney Function and Disease Nomenclature.[2] Among other aspects, we also highlighted the existence of a certain discrimination of classical terminology of Latin origin, such as the adjective “renal”.[3] It was also of great interest that the “Registro Latinoamericano de Diálisis y Trasplante Renal” [Latin American Registry of Dialysis and Renal Transplantation] and the Acute Kidney Injury Committee of the Sociedad Latinoamericana de Nefrología e Hipertensión (SLANH) [Latin American Society of Nephrology and Hypertension] also published a proposal for an Ibero-American consensus on nomenclature harmonisation.[4]

In the aforementioned initiative,[1] which is primarily focused on concepts essentially oriented towards chronic kidney disease (CKD), we have already pointed out that the introduction of new Anglo-Saxon terminology such as Acute Kidney Injury (AKI) has led to a clear dispersion in Spanish (from ẗfalloör ẗfalla, älteración, ẗfracaso, ïnsuficiencia, ẗdaño, ẗlesiónör even ïnjuria—an obvious anglicism).[5] The term ẗfallo renalör ẗfalla renal(for the English ẗfailure¨) contains contradictions in the KDIGO and SLANH guidelines’ own definitions (in one defined simply as duration of renal disease > three months and in the other as equivalent to "«fracaso» renal" or CKD G5 (with or without renal replacement therapy).[2,4] We had already emphasised that "«fracaso» renal agudo (FRA)", according to the KDIGO guidelines,[6] would be equivalent to AKI stage 3, so that the Spanish terms ẗdaño, injuria, lesión, fallo (o falla) renal agudoẅould not necessarily mean "«fracaso» renal". It was also suggested that "daño renal" or "injuria renalsẗhould noy be used (despite the names used by some committees) for various reasons, ranging from a lack of tradition to the fact that the term AKI is a purely cosmetic change, still defined by imprecise renal function and not by objective, function-independent markers of structural damage. It is also worth noting the introduction of the international concept of acute kidney disease (AKD) (decline in renal function more than seven days and less than three months), which refers by consensus to the transition after an acute episode towards the established criteria of CKD (Table 1).

Therefore, we understand that the conceptual evolution of the current model of acute kidney injury (AKI) (Fig. 1) has not only allowed new definitions to be introduced into the nomenclature, but has also broadened our knowledge of new mechanisms of kidney injury, which is why we believe that the early homogenisation of the terms ẗdisfunción, lesión, fracaso renal agudoïs essential.

This urgent call for attention is also linked to the existence of the "Acute Renal Failure" group of the Sociedad Española de Nefrología [Spanish Society of Nephrology], which has recently been interested (among other issues) in better understanding the role of nephrology in the management of kidney replacement therapies in intensive care units, but which should also take into account terminologically the broader and earlier concept of AKI. In fact, both patients with acute kidney function impairment [AKI 1-3 or "FRA" (AKI 3)] and AKI, as well as patients with impaired renal function without structural damage (p̈seudo worsening renal function" or "permissive AKI, in Anglo-Saxon terminology) are possible.[7,8] Therefore, and in order to respect widely used terms, we would like to stress that the term ẗfracaso renal agudoäand its acronym F̈RAs̈hould be reserved only for patients with KDIGO criteria (AKI 3). Given that creatinine is the only widely available biomarker, the term ¨ïnsuficiencia renal aguda(̈IRA [acute renal insufficiency], in its different stages 1-2-3, based on the inter-

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