Scientific letters

Initial Real-World Experience With PCSK-9 Inhibitors in Current Indications for Reimbursement in Spain

Experiencia inicial en la práctica clínica con los inhibidores de la PCSK-9 para las indicaciones actuales de financiación en España

To the Editor,

Proprotein convertase subtilisin/kexin 9 (PCSK-9) inhibitors are a new lipid-lowering therapy that has been conclusively demonstrated to reduce both low-density lipoprotein cholesterol (LDLc) and major cardiovascular events.[1,2] Evolocumab and alirocumab have been available for more than 1 year, and consequently there is still scarce evidence of their effectiveness in real-world practice under local or national reimbursement indications. The aim of our study was to describe the safety and effectiveness (in terms of LDLc reduction) of this treatment in the initial patients treated with either evolocumab or alirocumab in 5 institutions.

We performed a retrospective study of patients treated with evolocumab or alirocumab in 5 different hospitals in Spain in the first 6 months that these treatments were locally available. There are 3 current indications for reimbursement in Spain: familial hypercholesterolemia (FH) without cardiovascular disease (CVD) but LDLc > 100 mg/dL, CVD but LDLc > 100 mg/dL despite maximum tolerated lipid-lowering therapy and statin intolerance and LDLc > 100 mg/dL. Statin treatment was classified according to current guidelines.[3] Patients with intolerance were defined as those who abandoned statins due to adverse effects or did not tolerate high-doses.

Absolute and relative differences between biochemical determinations were calculated and differences were assessed by 1-way ANOVA and postestimation Bonferroni test. All analyses were performed using STATA 14.3 (Stata Corp 2009. College Station, TX: StataCorp LP).

We identified 98 patients referred for PCSK-9 treatment initiation but 1 patient refused to start it and 14 patients did not undergo a second blood test; therefore, safety and efficacy could be analyzed in 83 patients. The most frequent indication was CVD and LDLc > 100 mg/dL (74.5%); statin intolerance (16.3%) and FH and LDLc > 100 mg/dL (9.2%) were less frequent. No relevant differences were observed between the 3 patient subgroups other than a slightly higher prevalence of male sex and hypertension in patients with CHD (Table 1). Baseline statin use was very high and more than half of the patients were receiving ezetimibe. The most frequently used PCSK-9 inhibitor was evolocumab.

LDLc at the time when a PCSK-9 inhibitor was indicated (baseline LDLc) was 158.9 (60.3) mg/dL. The on-treatment second blood test was obtained at a median interval of 184.0 days (interquartile range, 93.5-310.5). The mean LDLc reduction was 55.5%. As shown in Figure 1, the treatment was effective all 3 groups and no differences were observed between them ($P = .88$). Nonetheless, patients treated with evolocumab had higher reductions than those treated with alirocumab: 67.7% vs 40.7% ($P < .001$), despite having the same baseline LDLc; only 9 patients received alirocumab 150 mg, baseline LDLc was 177.0 mg/dL, and LDLc reduction was equipotent to the 75 mg dose. No relevant adverse effects were reported; only 1 patient complained of a local site reaction after the seventh dose of evolocumab, which disappeared after we switched the site of administration.

Our initial experience with PCSK-9 inhibitors in real-world patients is in agreement with previously reported efficacy and safety.[1,2] We believe this reported experience is representative and relevant for daily clinical practice. PCSK-9 inhibitors are a completely novel and complementary strategy for LDLc reduction that can be used as monotherapy or combined with any other lipid-lowering drugs.[4] The positive results of randomized clinical trials[1,2] will most likely change guideline recommendations for drug combinations and upgrade recommendations for their use.

Evolocumab and alirocumab seem to have a similar effect on LDLc reduction at equipotent doses.[1,2] Alirocumab has 2 different presentations and most patients in the ODYSSEY Outcomes trial received the 75 mg dose[2]; therefore, final on-treatment LDLc was 53.3 mg/dL[2] in contrast to 30 mg/dL in the FOURIER trial.[1] Because most patients in our study treated with alirocumab received the 75 mg dose, the effect on LDLc reduction was lower than that for patients treated with evolocumab. The cost-effectiveness of PCSK-9 inhibitors in real-world practice is a matter of debate,[5] but we believe that our results could help the implementation of these therapies in daily practice.

As with every early experience with novel drugs, our study has the limitation of a small sample size and a retrospective and observational design. Moreover, treatment adherence to PCSK-9 inhibitors and the other lipid-lowering drugs was self-reported. Baseline LDLc was fairly high, which might reflect the fact that treatment was recommended in selected patients with very high LDLc.

In conclusion, the initial experience with evolocumab and alirocumab in real-world patients with uncontrolled LDLc supports the efficacy and safety of PCSK-9 inhibitors. Mean LDLc reduction was 55.5% and was statistically higher in patients treated with evolocumab vs alirocumab, as expected because of the doses chosen by the clinicians. Our study reinforces the efficacy of PCSK-9 inhibitors in daily clinical practice.

Table 1
Clinical features of the population according to indication for PSCK-9 therapy

	All	FH and LDL >100 mg/dL	CHD and LDL >100 mg/dL	Statin intolerance and LDL >100 mg/dL	*P*
Number, %	98	9 (9.2)	73 (74.5)	16 (16.3)	
Age	57.4 ± 11.4	44.3 ± 12.4	57.6 ± 11.3	61.2 ± 8.9	.64
BMI, kg/m²	28.5 ± 4.2	26.8 ± 4.7	28.6 ± 4.4	29.4 ± 1.7	.43
Male sex, %	62.2	44.4	68.5	43.8	.09
Hypertension, %	49.0	11.1	56.2	37.5	.02
Diabetes, %	22.5	0.0	27.4	12.5	.10
Current smoking, %	23.5	22.2	21.9	31.3	.72
Dyslipidemia, %	94.9	100.0	93.2	100.	.41
Previous CHD, %	81.6	22.2	91.8	68.8	< .01
Previous HF, %	9.2	11.1	11.0	0.0	.55
Previous stroke, %	6.1	0.0	8.2	0.0	.67
Peripheral arterial disease, %	8.2	0.0	9.6	6.3	.59
Atrial fibrillation, %	8.2	11.1	5.5	18.8	.20
Statin therapy, %	81.6	88.9	86.3	56.3	.02
Moderate-high dose statin, %	56.1	77.8	63.0	12.5	< .01
Ezetimibe therapy, %	52.0	22.2	56.2	50.0	.16
Statin plus ezetimibe, %	48.0	22.2	54.8	31.3	.18
Fibrates, %	23.1	0.0	23.5	30.0	.48
PCSK-9 inhibitor					
Alirocumab 75, %	34.7	11.1	38.4	31.3	.26
Alirocumab 150, %	9.2	22.2	9.6	0.0	.18
Evolocumab 140, %	56.1	66.7	52.0	68.7	.38
Baseline					
Total cholesterol, mg/dL	242.1 ± 74.6	346.4 ± 121.1	226.1 ± 54.1	257.0 ± 77.6	< .01[a]
LDLc, mg/dL	158.9 ± 60.3	259.0 ± 109.7	145.5 ± 37.3	163.9 ± 58.9	< .01[a]
HDLc, mg/dL	47.4 ± 14.4	67.1 ± 16.1	44.4 ± 11.3	50.2 ± 17.5	.01[a]
Triglycerides, mg/dL	186.8 ± 127.8	101.7 ± 50.7	197.7 ± 132.4	185.1 ± 123.0	.35
Fasting glucose, mg/dL	108.2 ± 29.7	89.1 ± 11.1	110.1 ± 31.2	110.6 ± 26.9	.26
HbA1c, %	5.8 ± 0.8	5.3 ± 0.3	5.9 ± 0.7	6.1 ± 1.7	.27
Hemoglobin, g/dL	14.6 ± 3.1	14.6 ± 0.6	14.7 ± 3.5	14.6 ± 1.5	.99
On-treatment					
Total cholesterol, mg/dL	151.8 ± 59.2	200.1 ± 102.0	140.3 ± 45.5	182.8 ± 71.0	< .01[b]
LDLc, mg/dL	71.7 ± 51.6	122.6 ± 96.4	62.4 ± 39.5	91.7 ± 56.9	< .01[a]
HDLc, mg/dL	48.3 ± 14.3	59.1 ± 20.7	45.7 ± 12.4	55.7 ± 15.7	.04[b]
Triglycerides, mg/dL	173.2 ± 157.4	93.1 ± 40.8	178.2 ± 162.2	189.6 ± 167.0	.37
Fasting glucose, mg/dL	113.2 ± 90.0	94.0 ± 19.9	121.1 ± 99.5	86.9 ± 581.0	.38
HbA1c, %	5.9 ± 0.8	5.1 ± 0.2	5.6 ± 1.7	5.3 ± 0.7	.12
Hemoglobin, g/dL	13.9 ± 3.1	14.8 ± 1.5	14.0 ± 2.7	12.8 ± 5.0	.44
LDLc reduction, %	55.5 ± 27.2	56.6 ± 25.1	56.2 ± 28.0	51.0 ± 25.3	.88
LDLc on target, %	61.5	57.1	65.6	41.7	.29

BMI, body mass index; CHD, coronary heart disease; FH, familial hypercholesterolemia; HDLc, high-density lipoprotein cholesterol; HF, heart failure; LDL, LDLc, low-density lipoprotein cholesterol; PCSK-9, proprotein convertase subtilisin/kexin 9.
Unless otherwise indicated, the data are expressed as No. (%) or mean ± standard deviation.
LDLc ontarget was considered < 100 mg/ dL in patients with FH and < 70 mg in the other 2 columns.
[a] For the comparison between FH and LDL > 100 mg/dL and the other 2 groups.
[b] For the comparison between CHD and LDL > 100 mg/dL and the other 2 groups.

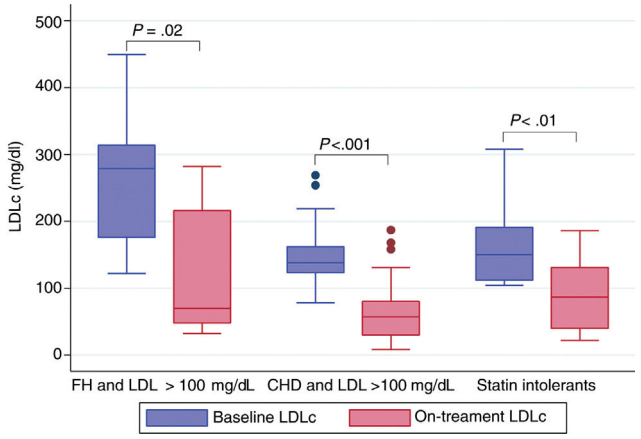

Figure 1. Baseline and on-treatment LDLc according to each indication. CHD, coronary heart disease; FH, familial hypercholesterolemia; LDLc, low-density lipoprotein cholesterol.

CONFLICTS OF INTEREST

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Successful Percutaneous Closure of a Complete Unroofed Coronary Sinus

Cierre percutáneo exitoso de comunicación interauricular tipo seno coronario destechado

To the Editor,

Unroofed coronary sinus is a rare form of atrial septal defect (ASD) in which the left atrium, coronary sinus, and right atrium are connected due to a defect in the roof of the coronary sinus.[1–4] The condition can remain undiagnosed because the clinical manifestations are nonspecific and the anatomy is hard to identify by transthoracic echocardiography.[2,3,5] The standard treatment is surgical closure.[3,4]

A 17-year-old woman with liver failure secondary to cavernous transformation of the portal vein was referred for cardiological assessment before liver transplant. The patient had been fitted with an intrahepatic transjugular portosystemic shunt to control portal hypertension. Transthoracic echocardiography revealed dilatation of the right ventricle, raising suspicion of ASD associated with unroofed coronary sinus. Magnetic resonance imaging confirmed the complete absence of the coronary sinus roof, accompanied by dilatation of the coronary sinus ostium and a Qp:Qs ratio = 1.9 (Figure 1A).

After a multidisciplinary assessment, the decision was taken to close the defect percutaneously, due to the liver failure and the patient's poor clinical status. Defect anatomy was defined by transesophageal echocardiography (TEE) and left-atrium angiography (Figure 1B and C and videos 1 and 2 of the supplementary data). The size of the coronary sinus ostium defect (in the inferoposterior region of the interatrial septum) was measured by angiography and 3D TEE (Figure 1D and video 3 of the supplementary data). The maximum initial diameter was 17-18 mm, and the stop-flow diameter determined by fluoroscopy and TEE was 20-21 mm. The device selected for the procedure was a 21 mm Figulla-Flex II ASD occluder (FFO, Occlutech GmbH; Jena, Germany), which was advanced through a long sheath to the left atrium. The left disc was opened in the left atrium, the device waist was positioned in the coronary sinus ostium, the right disc was opened in the right atrium, and the device was released without incident. Nevertheless, some minutes later, the device migrated to the left ventricle and was retrieved by retrograde capture from the femoral artery. The atrial defect subsequently measured 23-24 mm on TEE, with the increase possibly due to the passage of the device through the defect and the rigid guidewire used for the second implant. For the second attempt, a 27 mm Figulla-Flex II device was selected and was released without subsequent events (Figure 2A-D and videos 4-6 of the supplementary data).