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Research Article

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PCSK-9 Inhibitors in a Real-World Setting and a Comparison Between Alirocumab and Evolocumab in Heterozygous FH Patients

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Abstract

A real-world setting study of familial hypercholesterolemia (FH) patients who received Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in a specialized referral center in Mexico City. Ten patients between the ages of 18 and 70 years, with a diagnosis of FH according to Dutch Lipid Clinic Network (DLCN) criteria, with failure to achieve their Low-density lipoprotein Cholesterol (LDL-C) goals, and with standard therapy between 2016 and 2017 enrolled in a simple randomization in which a group of 5 participants received alirocumab (75 mg every 2 weeks) and the remaining 5 patients received evolocumab (140 mg every 2 weeks). Comparative analysis was made, analyzing the means of LDL at baseline at 4, 6, and 12 weeks. The evolocumab group had an average initial LDL-C of 277 mg/dL, which, after 12 weeks of treatment, was significantly reduced to 116 mg/dL; $P = 0.04$ (95% confidence interval [CI]: 11.5–310.9). The alirocumab group with a mean initial LDL-C of 229 mg/dL showed a reduction of LDL-C levels at 12 weeks of treatment to 80 mg/dL; $P = 0.008$ (95% CI: 63.8–233.7). In conclusion, PCSK9 inhibitors are an excellent treatment option in patients with FH who do not reach their LDL-C goals

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with standard therapy or due to intolerance to the standard therapy. There is no difference in the lipid-lowering effect between both PSCK9 inhibitors.

Key Words: PCSK9 inhibitors, alirocumab, evolocumab

Familial hypercholesterolemia (FH) is a genetic disorder of lipid metabolism that affects around 0.4% of people, which is estimated to be between 14 to 34 million people worldwide [1, 2]. It is the disorder most strongly associated with cardiovascular disease (CVD). In its heterozygous form, patients develop CVD at around age 55 and 60 in men and women, respectively, while patients with the homozygous form of Familial hyoercholesterolemia (FH) (total cholesterol [TC] levels between 12 and 30 mmol/L) typically develop CVD in the early stages of life. It is estimated that in patients with FH, the risk of developing CVD increases up to 10 times [1, 3].

The most used criteria for the diagnosis of FH are those of the Dutch Lipid Clinic Network (DLCN). However, several other diagnostic criteria have been proposed to define FH (Simon Broome's registry criteria or the World Health Organization's criteria). The characteristics that permeate all of them is a markedly elevated level of low-density lipoprotein cholesterol (LDL-C) in the patient and a family history of high levels of LDL-C or CVD. Other characteristics found in FH patients are xanthomas, xanthelasmas, corneal arch, and genetic mutations associated with lipid metabolism [4].

The treatment goal, according to the 2019 European Guidelines for Cardiology and Atherosclerosis, in patients with FH with established CVD or another major risk factor classified as very high risk is the reduction of ≥ 50% from baseline LDL-C and LDL-C levels < 55 mg/dl. In contrast, patients with FH without any other risk factor or established CVD have a goal of reducing LDL-C from baseline by ≥ 50% and achieving levels of < 70 mg/dl. In children of 10 years or older, treatment is recommended to reduce LDL-C to < 135 mg/dl [1].

There are several treatments to lower LDL-C levels in patients with FH, including statins, ezetimibe, bile acid sequestrants, and, the most recent, protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Statins are the mainstream treatment in FH patients since they reduce LDL-C levels by 50% to 58% [1]. Despite statin efficiency, a high fraction of cases do not reach the desired goal [5]. On the other hand, a statin intolerance of 10% to 15% has been reported mainly due to statin-related myositis [6]. Tailor-made treatments have been implemented for each patient to optimize LDL-C reduction.

PCSK9 increases the degradation of the LDL receptor, subsequently decreasing the uptake of circulating LDL by the hepatocyte and increasing plasma LDL-C levels [7]. PCSK9 inhibitors increase the cell membrane of the LDL receptor and reduce LDL-C up to 50% to 65%, obtaining 65.29 mg/dl on average on randomized controlled studies [4, 8].

There are 2 PCSK9 inhibitors on the market (alirocumab and evolocumab). The use of alirocumab, but not evolocumab, has been shown to decrease the risk of mortality by 17% compared with control [9]. Currently, there are no reports that directly compare the potency of both PSCK9 inhibitors on the reduction of LDL-C in a real-world setting [10].

Several clinical considerations can affect patient adherence in the use of PCSK9 inhibitors, such as the route of application (which is subcutaneous), the lack of long-term studies with sufficient power to demonstrate cardiovascular safety and outcomes, and the high cost of use. The cost of PCSK9 inhibitors is estimated to be $12 000 to $14 000 dollars, compared with less than $100 annually for a generic statin [11–13] This leads us to consider whether the use of PCSK9 inhibitors in clinical practice in real-life settings will have lipid-lowering efficacy and long-term adherence consistent with that demonstrated in randomized controlled studies [14].

There is little information on the efficacy, tolerance, and adherence to PCSK9 inhibitors in daily clinical practice [15]. The objective of this study is to report the results of the use of PCSK9 inhibitors in clinical practice administered to patients with FH coupled with statin treatment and to compare both PCSK9 inhibitors available on the market in a specialized center in Mexico City.

Material and Methods

A prospective study was conducted to analyze a cohort of patients who were simply randomized to receive PCSK9 inhibitors for FH treatment. Ten patients with the following inclusion criteria were studied: (1) age of 18–70 years; (2) diagnosis of FH according to DLCN criteria, with a score of ≥ 6; (3) failure to achieve the desired LDL-C goal with a high-intensity statin and/or ezetimibe or due to statin intolerance (using the McGuill short questionnaire for pain) or use of 3 different statins at the maximum dose; and (4) start of PSCK9 inhibitor treatment between 2016 and 2017. Randomization was performed to receive alirocumab 75 mg every 2 weeks or evolocumab 140 mg

every 2 weeks, according to the time of diagnosis in the Endocrinology Service of the Medical Specialties Unit of the Ministry of National Defense. In this specialized center, patients were trained on how to administer the subcutaneous injections, and during their treatment, telephone calls were made to patients to ensure that the medication was used. The medical team performed a follow-up with all the patients at specific time points (4, 6, and 12 weeks; 6 and 12 months) during the 1-year study, with a lipid profile, as well as with complementary studies. The use of triple therapy with statin therapy, ezetimibe, and PCSK9 inhibitors was compared against PCSK9 inhibitor monotherapy in patients with statin intolerance.

All medical data stored in electronic devices were analyzed with proper care by using IBM SPSS statistics v.21 program. The models of analysis used to check the heterogeneity of 2 independent samples were the Mann-Whitney U nonparametric test and the student's *t*-test.

Previous CVD history, such as acute myocardial infarction, unstable angina, and cerebral vascular disease, was taken on account as secondary outcomes. The presence of carotid plaques was evaluated by carotid doppler in all patients.

Results

Ten patients were studied, half of whom received alirocumab and the other half of whom received evolocumab. (Table 1) Of these, 60% were men. Of the FH patients studied, 40% had a history of established CVD, specifically acute myocardial infarction (3 patients) and cerebral vascular disease (1 patient). No new CV event occurred during the follow-up of the patients. One patient presented evidence of unstable plaque on carotid Doppler. The study showed a reduction in the lumen of 71% and 43% on the left internal carotid and right internal carotid, respectively.

A genetic study was performed in 2 of the patients with the following results: c.249delTinsGG mutation in heterozygous state of the LDL receptor gene and a p.P109R mutation in heterozygous state mutation of the LDL receptor gene. These 2 mutations are studied in more detail in a case of compound heterozygous FH [16].

We compared the LDL-C means at baseline and at 4, 6, and 12 weeks of treatment using a *t*-test for related samples. The evolocumab group presented an initial mean LDL-C of 277 mg/dl that, after 12 weeks of treatment, significantly reduced to 116 mg/dl; $P = 0.04$ (95% CI: 11.5–310.9). The alirocumab group started with an LDL-C of 229 mg/dl, and at 12 months of treatment there was a significant decrease to 80 mg/dl; $P = 0.008$ (95% CI: 63.8–233.7); this significant reduction is evident from 8 weeks of treatment and persists throughout the treatment (Table 2). The average decrease at 12 weeks of treatment was 186 mg/dl and 149 mg/dl for the evolocumab and alirocumab groups, respectively. In the analysis by gender (Table 2), we found a significant decrease in LDL-C with both treatments and there is no difference in LDL-C levels between genders before or after treatment (Fig. 1).

A Mann-Whitney U nonparametric test was performed to contrast the difference between evolocumab and alirocumab at the beginning and at 12 weeks of treatment, with $P = 0.548$ (in both cases).

Of the 4 patients with established CVD (very high risk), 100% of them achieved their LDL-C goals (< 55 mg/dl) at the endpoint; however, only 3 (75%) maintained these goals 24 months later. In contrast, with the remaining 6 patients with absent CVD, only 3 of them (50%) reached their LDL-C goals of < 70 mg/dl, although the target to reduce ≥50% of LDL-C from baseline was met.

By calculating every individual patient's percentage of reduction of LDL-C in both groups and comparing them by using a Mann-Whitney U comparative test, we proved that there is not a difference between the alirocumab and evolocumab groups (Tables 3 and 4).

Discussion and Conclusions

This study is one of the few studies in a real-world setting that explores the efficacy and tolerance of FH patients who are treated with PCSK9 inhibitors as an adjuvant treatment

Table 1. Demographic characteristics of patients and biochemical changes over time

	Alirocumab Group	Evolocumab Group	Both Groups
Median age in years (IQR)	49 (38–59)	63 (43–68)	51 (39–65)
Men, (n %)	3 (30)	3 (30)	6 (60)
Baseline LDL-C (IQR)	205 (183–287)	315 (148–387)	235 (187–326)
Median LDL-C at 4 weeks of treatment (IQR)	100 (86–115)	94 (45–136)	97 (73–122)
Median LDL-C at 6 weeks of treatment (IQR)	55 (48–79)	98 (84–133)	84 (54–107)
Median LDL-C at 12 weeks of treatment (IQR)	92 (50–104)	92 (74–170)	92 (60–103)

Total n = 10, LDL-C expressed in mg/dl. Abbreviations: IQR, Interquartile range; LDL-C, Low-density lipoprotein Cholesterol.

Table 2. Comparison of LDL-C levels between the two treatment and gender groups

	Baseline Mean LDL-C	4-Week Mean LDL-C	*P*-value	12-week Mean LDL-C	*P*-value
Evolocumab	277	91 (95% CI: 43.2–328.7)	0.022	116 (95% CI 11.15–310.9)	0.04
Alirocumab	229	100 (95% CI: 57.7–199.4)	0.007	80 (95% CI 63.8–233.7)	0.008
Both treatment groups	253	95 (95% CI: 92.3–222.2)	0.00	98 (95% CI 88.7–221.2)	0.00
Female	298			92 (95% CI 55.5–356.4)	0.02
Male	223			102 (95% CI 35.6–206.3)	0.015

LDL-C expressed in mg/dl. Abbreviations: CI, Confidence Interval; LDL-C, Low-density lipoprotein Cholesterol.

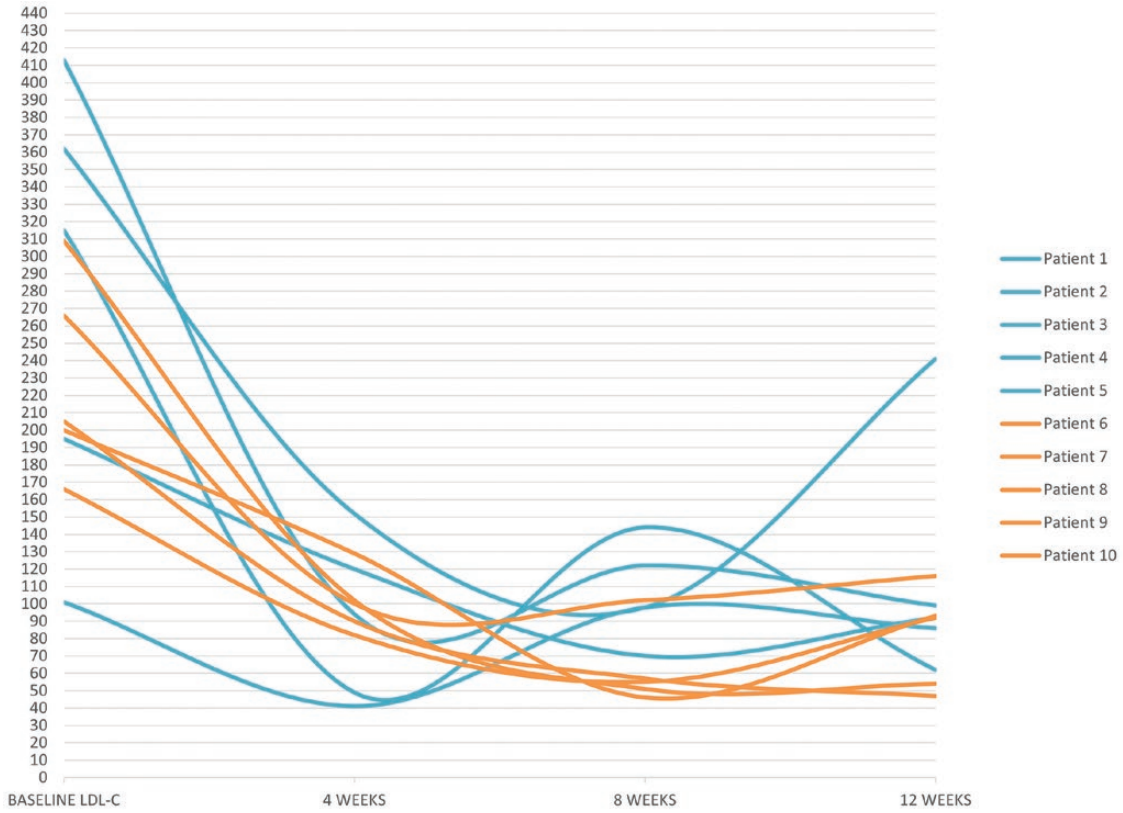

Figure 1. Graphic of Low-density lipoprotein Cholesterol (LDL-C) levels of all patients throughout the 12 weeks of treatment. LDL-C levels are in mg/dL. The evolocumab group is shown in blue and the alirocumab group is shown in red.

to high-intensity statins therapy or monotherapy in patients with statin intolerance.

The observations made on the therapeutic effects of PCSK9 inhibitors were excellent. There was a 66% average reduction in initial LDL-C, and it was maintained throughout 12 months. Similar reports are made in other studies evaluating the effect of PCSK9 inhibitors in clinical practice [17]. Both commercially available PCSK9 inhibitors have similar lipid-lowering effects, with a significant reduction on LDL-C.

The patients with statin intolerance who were treated with PCSK9 inhibitor monotherapy achieved their LDL-C reduction goals from baseline levels without adverse effects. Combined treatment with statin, ezetimibe, and PCSK9 inhibitors have a greater effect in reducing LDL-C ($P = 0.037$) compared with PCSK9 inhibitors alone, as previously reported in Gamera-Boers et al and Rallidis LS et al [15, 18].

We found a high percentage of treatment discontinuation of PCSK9 inhibitors, probably due to the control of this medication, its high cost, and the need for regular monitoring of the patient. This has been observed in other studies such as the study by Kathleen A. Fairman et al, in which a cohort of 390 patients with PCSK9 inhibitor treatment was analyzed in clinical practice. Of the patients analyzed, 39.8% did not continue treatment after 60 days because it required authorization and periodic evaluation in order to continue with PCSK9 inhibitor treatment [17].

Table 3. Individual percentage of reduction of LDL-C levels in the alirocumab group

Patient	Baseline LDL-C	Final LDL-C	Individual Percentage of Reduction, %
1	200	99	69
2	266	151	43
3	309	151	51
4	166	40	75
5	205	113	44

n = 5; LDL-C expressed in mg/dl. Abbreviations: CI, Confidence Interval; LDL-C, Low-density lipoprotein Cholesterol.

Table 4. Individual percentage of reduction of LDL-C levels in the evolocumab group

Patient	Baseline LDL-C	Final LDL-C	Individual Percentage of Reduction, %
1	315	89	71
2	362	197	45
3	195	61	68
4	101	56	44
5	413	99	76

n = 5; LDL-C expressed in mg/dl. Abbreviations: CI, Confidence Interval; LDL-C, Low-density lipoprotein Cholesterol.

The percentage of suspension or nonadherence to treatment was higher than that reported in other studies (between 8% and 10%) [15, 18].

PCSK9 inhibitors are an excellent treatment option for patients with FH who do not reach their LDL-C goals with a high-intensity statin and/or ezetimibe, or patients with statin intolerance. There is no difference in the lipid-lowering effect between the 2 PSCK9 inhibitors available on the market, and they have a significant positive response in achieving LDL-C treatment goals in patients with a high cardiovascular risk. There is a significantly better response to LDL-C reduction in patients with triple therapy compared with monotherapy with PCSK9 inhibitors, as has been shown in other studies in heterozygous patients.

Among the disadvantages of this study is the short period of treatment to analyze persistence and attachment to the treatment by the patient. And persistence of healthcare workers and affiliates to monitor patient's administration of treatment and follow-up. Another limitation was the number of patients studied, since they are patients treated in a single medical center and who have a disease with a low incidence rate; however, of the patients treated in our clinical practice, the majority of patients responded adequately to statins and achieved their therapeutic goals in LDL-C reduction.

Patients with FH should be evaluated and educated about their disease, the benefits of adequate treatment to improve adherence and to ensure the clinical benefit of PCSK9 inhibitors in long-term therapies, and the consequences of suspension. Greater experience in daily clinical practice and longer therapeutic studies with PCSK9 inhibitors in patients with FH are required to assess the long-term reduction in cardiovascular risk.

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Additional Information

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References and Notes

1. Mach F, Baigent C, Catapano AL, et al.; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41(1):111–188.
2. Goldberg AC, Gidding SS. Knowing the prevalence of familial hypercholesterolemia matters. *Circulation.* 2016;**133**(11):1054–1057.
3. Nordestgaard BG, Chapman MJ, Humphries SE, et al.; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J.* 2013;**34**(45):3478–390a.
4. Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. *Nat Rev Dis Primers.* 2017;**3**:17093.
5. Merchán A, Ruiz ÁJ, Campo R, et al. Hipercolesterolemia familiar: artículo de revision. *Rev Colomb Cardiol.* 2016;**23**(S4):4–26.
6. Stroes ES, Thompson PD, Corsini A, et al.; European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J.* 2015;**36**(17):1012–1022.
7. Ogura M. PCSK9 inhibition in the management of familial hypercholesterolemia. *J Cardiol.* 2018;**71**(1):1–7.
8. Li C, Lin L, Zhang W, et al. Efficiency and safety of proprotein convertase subtilisin/kexin 9 monoclonal antibody on hypercholesterolemia: a meta-analysis of 20 randomized controlled trials. *J Am Heart Assoc.* 2015;**4**(6):e001937.
9. Guedeney P, Giustino G, Sorrentino S, et al. Efficacy and safety of alirocumab and evolocumab: a systematic review and

meta-analysis of randomized controlled trials. *Eur Heart J*. 2019;ehz430. Doi: 10.1093/eurheartj/ehz430.

10. McDonagh M, Peterson K, Holzhammer B, Fazio S. A systematic review of PCSK9 inhibitors alirocumab and evolocumab. *J Manag Care Spec Pharm*. 2016;**22**(6):641–653q.
11. Silverman E. New cholesterol meds may lower heart risks, but will they break the bank? *Wall Street J*. 2015. ProMED-mail website. https:// blogs.wsj.com/pharmalot/2015/03/20/new-cholesterol-meds-may- lower-heart-risks-but-will-they-break-the-bank/. Accessed July 10, 2017.
12. Arrieta A, Page TF, Veledar E, Nasir K. Economic evaluation of PCSK9 inhibitors in reducing cardiovascular risk from health system and private payer perspectives. *PLoS One*. 2017;**12**(1):e0169761.
13. Kazi DS, Moran AE, Coxson PG, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercho- lesterolemia or atherosclerotic cardiovascular disease. *JAMA*. 2016;**316**(7):743–753.
14. Hlatky MA, Kazi DS. PCSK9 inhibitors: economics and policy. *J Am Coll Cardiol*. 2017;**70**(21):2677–2687.
15. Galema-Boers AMH, Lenzen MJ, Sijbrands EJ, Roeters van Lennep JE. Proprotein convertase subtilisin/kexin 9 inhibition in patients with familial hypercholesterolemia: initial clinical experience. *Clin Lipidol*. 2017;**11**(3):674–681.
16. Ceballos-Macías JJ, Madriz-Prado R, Vázquez Cárdenas NA, et al. Use of PCSK9 inhibitor in a mexican boy with compound heterozygous familial hypercholesterolemia: a case report. *J Endocr Soc*. 2020;**4**(2):bvz018.
17. Fairman KA, Davis LE, Sclar DA. Real-world use of PCSK-9 inhibitors by early adopters: cardiovascular risk factors, statin co-treatment, and short-term adherence in routine clinical practice. *Ther Clin Risk Manag* 2017;**13**: 957–965.
18. Rallidis LS, Skoumas I, Liberopoulos EN, et al. PCSK9 inhibitors in clinical practice: novel directions and new experiences. *Hell J Cardiol*. Doi: 10.1016/j.hjc.2019.10.003.