



Real-World Efficacy of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors (PCSK9i) in Heterozygous Familial Hypercholesterolemia Patients Referred for Lipoprotein Apheresis

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Statistical Analysis C
Data Interpretation D
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Background:

A small proportion of familial hypercholesterolemia (FH) patients can adequately control this condition, although achieving the recommended targets for low-density lipoprotein cholesterol (LDL-c) levels remains a challenge. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are new and potent lipid-lowering drugs. However, there is scarce literature on real-world data about their use in patients with FH.

Material/Methods:

We examined the reduction in LDL-c levels from the baseline, after PCSK9i initiation in heterozygous familial hypercholesterolemia patients referred for lipoprotein apheresis in our regional lipid clinic. The study was conducted from March 2018 to September 2019, the period immediately after PCSK9i reimbursement was available in France. PCSK9i was added on top of the patients' maximal tolerated lipid-lowering regimens.

Results:

The study had 123 patients with heterozygous FH. The mean age of the patients was 59±11 years. The mean baseline LDL-c for all the participants was 277±78 mg/dl. It was 283±81 mg/dl in the PCSK9i monotherapy group (n=83), 247±68 mg/dl in the PCSK9i plus ezetimibe group (n=12), and 264±78 mg/dl in the PCSK9i plus statin and ezetimibe group (n=28). The mean decrease observed in the LDL-c level from baseline was 136±70 mg/dl (n=123), 125±60 mg/dl (n=83), 103±77 mg/dl (n=12), and 175±70 mg/dl (n=28), respectively.

Conclusions:


An overall reduction of 49.1% from the baseline LDL-c was observed in the heterozygous FH population after PCSK9i initiation in a real-world experience. The group treated with PCSK9i ezetimibe plus statin showed further reduction of their LDL-c levels with a better responder rate, achieving the target 50% reduction in LDL-c from the baseline.

Keywords:

Cholesterol, LDL • Dyslipidemias • Proprotein Convertases

Full-text PDF:

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Background

Familial hypercholesterolemia (FH) is a common, autosomal dominant hereditary disease caused by mutations in the genes encoding key proteins involved in the low-density lipoprotein (LDL) receptor's (LDLR) endocytic and recycling pathways. The LDLR gene encodes the LDLR, the apolipoprotein B gene encodes apolipoprotein B (the ligand of the LDL receptor), and the PCSK9 gene encodes a serine protease (proprotein convertase subtilisin/kexin type 9 or PCSK9), which plays a role in the degradation of the LDLR [1]. Mutations in the LDLR adaptor protein 1 gene are responsible for the recessive form of the disease [2]. However, FH is an underdiagnosed and undertreated genetic disorder that results in premature mortality and morbidity due to atherosclerotic disease. Myocardial infarction, stroke, or other cardiovascular events could be the first clinical presentation of FH [3]. European guidelines classify FH patients at high cardiovascular risk and the optimal target for low-density lipoprotein cholesterol (LDL-c) is ≤ 70 mg/dl with $\geq 50\%$ reduction from the level at baseline [4]. Reaching these LDL-c goals in clinical practice remains a challenge for physicians.

All the statins have proven their effectiveness in significantly lowering LDL-c levels (upregulating the LDL receptor in the liver and peripheral tissues) and are recommended as first-line therapy. Nevertheless, muscle and joint pain are common adverse effects associated with statin therapy, which lead to an interruption of medical treatment in real-life practice. PCSK9 inhibitors (PCSK9i) have recently emerged as novel medications indicated for patients who cannot tolerate statins, and cannot achieve the required optimal LDL-c levels [5].

Clinical trials have shown that PCSK9i can effectively reduce the baseline LDL-c levels by 60% on average, when used alone or combined with other lipid-lowering agents [4]. Current trials are investigating PCSK9i as an alternative therapeutic option for patients undergoing lipoprotein apheresis, as it shows a synergistic effect leading to a drop in extracorporeal apheresis sessions and lipoprotein apheresis withdrawal (in some cases) [6]. Concerns regarding the inter-individual variability, FH mutations, LDLR abnormalities, and the importance of pre-treatment with statins in patients on PCSK9i have been raised, as all these factors are well-known predictors of the efficacy of lipid-lowering drugs. In the Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities (TESLA) [7], neither a single autosomal recessive hypercholesterolemia patient nor a single null/null LDLR homozygote patient responded to evolocumab. Similar results were observed in larger numbers of patients for both these patient categories in the Trial Assessing Long-Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders (TAUSSIG) study [8]. Robinson et al reported that PCSK9i is more effective in patients with higher levels of circulating PCSK9 stimulated by previous statin therapy [9].

In addition, the failure to respond to PCSK9i occurs more frequently, as PCSK9i is more commonly prescribed [10].

The real-world efficacy of PCSK9i regarding patients' characteristics and the severity of LDL-c levels are not known since the vast majority of randomized controlled trials have been conducted on patients receiving combination therapy (PCSK9i and statin), and patients with low LDL-c before treatment [11-14]. Therefore, we aimed to investigate the variation in LDL-c levels after initiation of PCSK9i, either as monotherapy, or in combination with previously prescribed ezetimibe or statin plus ezetimibe in a real-life cohort study of severely dyslipidemic heterozygous FH patients referred for lipoprotein apheresis. In this study population, the baseline LDL-c level was one of the highest reported in literature.

Material and Methods

Study Design and Population

An observational single-center cohort study was conducted on patients referred for lipoprotein apheresis at our Lipid, Atherosclerosis, and Preventive Cardiology Clinic at Rangueil University Hospital, Toulouse, France between March 2018 and September 2019. Patients were eligible for participating in the study if they were diagnosed with FH according to the Dutch Lipid Clinic Network score [15]. In France, alirocumab is reimbursed only for patients treated for primary prevention (LDL-c ≥ 300 mg/dl) or secondary prevention (LDL-c ≥ 200 mg/dl) in the setting of an experienced lipoprotein apheresis center. Therefore, patients with these baseline LDL-c levels were requested to participate in the study. The patients were divided into 3 groups based on their real-world prescriptions in this observational study: those treated with PCSK9i only, those treated with PCSK9i in addition to the preexisting ezetimibe therapy, and those treated with PCSK9i in addition to the preexisting statin plus ezetimibe therapy. Alirocumab monotherapy was initiated in the statin-intolerant patients. Statin intolerance was defined as an inability in the past to tolerate 2 or more statins (1 statin at the lowest daily starting dose). Alirocumab was added on top of a maximal tolerated lipid-lowering regimen in patients taking either ezetimibe or a statin plus ezetimibe. The alirocumab was prescribed as a 150 mg subcutaneous injection administered every 2 weeks.

Data Collection and End Points

During the initial visit, a physician performed a detailed physical examination, and recorded family and personal medical histories of the participants. The issues of incorrect injection techniques and non-adherence to treatment were eliminated, as the medical team supervised the injections. Full lipid

Table 1. Baseline characteristics of the study population.

| | Whole population (n=123) | PCSK9i (n=83) | PCSK9i plus ezetimibe (n=12) | PCSK9i plus statin and ezetimibe (n=28) |
|---|-----------------------------|------------------|---------------------------------|--|
| Age (years±SD) | 59±11 | 58±12 | 62±11 | 57±10 |
| Sex | | | | |
| Male, n (%) | 66 (53.7%) | 41 (49.4%) | 5 (41.7%) | 20 (71.4%) |
| Female, n (%) | 57 (46.3%) | 42 (50.6%) | 7 (58.3%) | 8 (28.6%) |
| Familial hypercholesterolemia, n (%) | 123 (100.0%) | | | |
| Without known ASCVD, n (%) | 29 (23.6%) | 25 (30.1%) | 3 (25.0%) | 1 (3.6%) |
| With ASCVD, n (%) | 94 (76.4%) | 58 (69.9%) | 9 (75.0%) | 27 (96.4%) |
| Atherosclerotic disease | | | | |
| Coronary artery disease, n (%) | 82 (66.7%) | 50 (60.2%) | 9 (75.0%) | 23 (82.1%) |
| Ischemic stroke, n (%) | 3 (2.4%) | 3 (3.6%) | 0 (0.0%) | 0 (0.0%) |
| Peripheral artery disease, n (%) | 12 (9.8%) | 10 (12.0%) | 0 (0.0%) | 2 (7.1%) |
| Cardiovascular risk factors | | | | |
| Hypertension, n (%) | 30 (24.4%) | 21 (25.3%) | 4 (33.3%) | 5 (17.8%) |
| Diabetes mellitus, n (%) | 9 (7.3%) | 7 (8.4%) | 1 (8.3%) | 1 (3.6%) |
| Current smokers, n (%) | 4 (3.3%) | 4 (4.8%) | 0 (0.0%) | 0 (0.0%) |
| Mean total cholesterol level (mg/dl±SD) | 361±83 | 373±83 | 332±66 | 337±82 |
| Mean triglycerides (mg/dl±SD) | 168±69 | 175±73 | 167±59 | 143±52 |
| Mean HDL-c (mg/dl±SD) | 52±13 | 53±14 | 50±10 | 48±13 |
| Mean LDL-c level (mg/dl±SD) | 277±78 | 283±81 | 247±68 | 264±78 |

ASCVD – atherosclerotic cardiovascular disease; HDL-c – high-density lipoprotein cholesterol; LDL-c – low-density lipoprotein cholesterol; n – number of patients; PCSK9i – proprotein convertase subtilisin/kexin type 9 inhibitors; SD – standard deviation.

panels at the initiation of the PCSK9i therapy (baseline LDL-c) and 6 months after the initiation of the PCSK9i treatment were collected. Based on the 2019 European Society of Cardiology (ESC) guidelines for FH management, ≥50% reduction from the LDL-c baseline was considered a satisfactory response to PCSK9i in this study. The main outcome was the variation in LDL-c levels, 6 months from the baseline levels after initiation of the PCSK9i treatment in the 3 groups of patients. None of the patients had received a statin without ezetimibe before inclusion in the study. The secondary outcome was the percentage of responders at 6 months (ie, ≥50% drop in LDL-c).

Statistical Analysis

Continuous data were summarized as means and standard deviations, and categorical variables were summarized as counts and percentages. The continuous variables were compared between the 3 groups through an analysis of variance (ANOVA). The bivariate associations with the categorical variables were studied with the chi-square test or Fisher's exact test as appropriate.

ANOVA was used to compare the mean change in LDL-c levels between the groups. A multivariate linear regression analysis was conducted for studying percentage variations in the

LDL-c levels from baseline in the 3 groups. The patients treated with PCSK9i alone were considered the reference group. A multivariate logistic regression analysis was conducted to study the satisfactory response to treatment as a dependent variable. The multivariate analyses were adjusted for age, sex, type of prevention (primary or secondary), and the baseline lipid panel. A *P* value <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 20, (SPSS Inc., IBM, Chicago, IL, USA).

The patients were seen at our clinic within a regular follow-up; therefore, approval from the Ethics Committee was not needed. The patients gave oral consent for participation in the study, which followed the institution's ethical rules.

Results

A total of 123 patients with heterozygous FH were included in the study (**Supplementary Online Table 1**). They were divided into 3 groups. The baseline characteristics of these participants are shown in **Table 1**. Their mean age was 59±11 years; there were 66 (53.7%) men and 57 (46.3%) women. Four (3.3%) patients were smokers, 30 (24.4%) patients had systemic hypertension, 9 (7.3%) patients had diabetes mellitus,

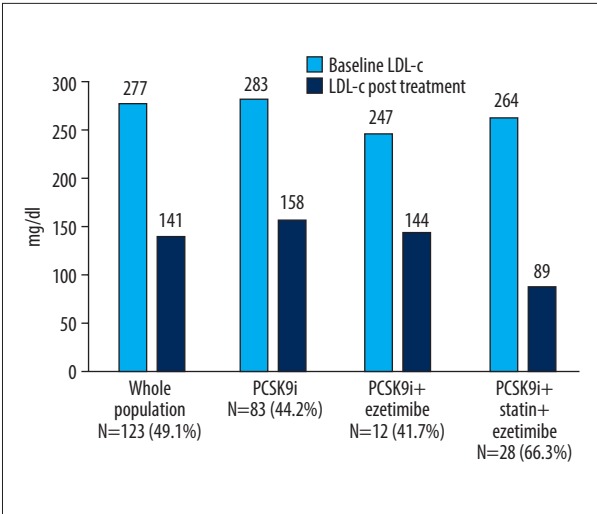


Figure 1. Low-density lipoprotein cholesterol reduction (%) from the baseline after PCSK9i initiation. PCSK9i – proprotein convertase subtilisin/kexin type 9 inhibitor.

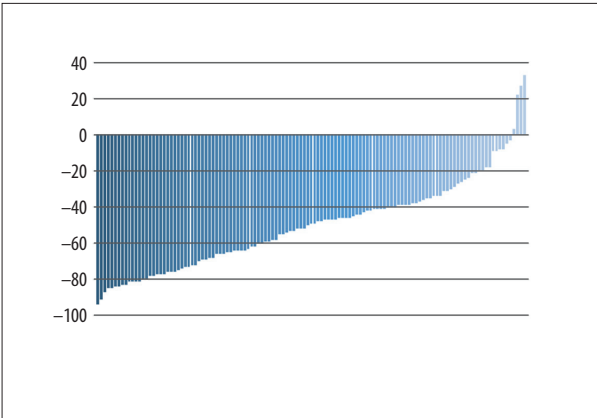


Figure 2. Waterfall plot of the variation (%) in low-density lipoprotein cholesterol of 123 heterozygous familial hypercholesterolemia patients after initiation of PCSK9i. PCSK9i – proprotein convertase subtilisin/kexin type 9 inhibitor.

Table 2. Analysis of variance (ANOVA) comparing the reduction in mean low-density lipoprotein cholesterol between the 3 groups after adding PCSK9i.

| | Mean variation in LDL-c (mg/dl±SD) | Compared to | 95% CI | P value |
|-----------------------------|------------------------------------|-----------------------------------|---------------------------------|----------------|
| PCSK9i | 125±60 | PCSK9i+statin PCSK9i+ezetimibe | (-0.85; -0.15) (-0.28; 0.72) | 0.002 0.86 |
| PCSK9i+ezetimibe | 103±89 | PCSK9i PCSK9i+statin | (-0.72; 0.28) (-1.28; -0.17) | 0.86 0.006 |
| PCSK9i+statin and ezetimibe | 175±72 | PCSK9i PCSK9i+ezetimibe | (0.15; 0.85) (0.17; 1.28) | 0.002 0.006 |

CI – confidence interval; HDL-c – high-density lipoprotein cholesterol; LDL-c – low-density lipoprotein cholesterol; PCSK9i – proprotein convertase subtilisin/kexin type 9 inhibitors.

28 (22.8%) patients were taking statin and ezetimibe prior to the PCSK9i initiation, and 95 (77.2%) patients were statin-intolerant. Of the statin-intolerant patients, 12 (9.8%) patients were taking ezetimibe prior to the PCSK9i initiation and 83 (67.5%) patients did not receive any lipid-lowering agents before the PCSK9i initiation. Twenty-nine (23.6%) patients were being treated for primary prevention. Among the 94 (76.4%) patients treated for secondary prevention, 82 (87.2%) patients had coronary artery disease, 3 (3.2%) patients had a history of ischemic stroke, and 12 (12.8%) patients had peripheral artery disease. The overall mean total cholesterol, LDL-c, high-density lipoprotein cholesterol (HDL-c), and triglyceride baseline levels were 361±83 mg/dl, 277±78 mg/dl, 52±13 mg/dl, and 168±69 mg/dl, respectively.

The mean baseline LDL-c level dropped from 277±78 mg/dl to 141±84 mg/dl in the entire study population, accounting for a 49.1% reduction. The mean baseline LDL-c level showed

a 44.2% reduction (from 283±81 mg/dl to 158±83 mg/dl) in the PCSK9i monotherapy group (n=83), a 41.7% reduction in LDL-c (from 247±68 mg/dl to 144±100 mg/dl) in the PCSK9i plus ezetimibe group (n=12), and a 66.3% reduction in LDL-c (from 264±78 mg/dl to 89±57 mg/dl) in the PCSK9i plus statin and ezetimibe group (n=28) (**Figures 1, 2**). Statistical analysis (ANOVA) showed a statistically significant difference in the mean LDL-c reduction between the PCSK9i plus statin and ezetimibe group compared to the other 2 groups (PCSK9i only, $P=0.002$, and PCSK9i plus ezetimibe, $P=0.006$), while no significant difference was noted between the PCSK9i only and PCSK9i plus ezetimibe groups (**Table 2**). A secondary multivariate analysis using linear regression (% of LDL-c reduction=dependent variable) showed a significant correlation between the statin group (PCSK9i plus statin and ezetimibe) and the percentage of LDL-c reduction ($\beta=-20.21$, confidence interval [CI] [-30.46 to -9.95], $P<0.0001$).

Table 3. A comparison of the responder rate between the 3 groups.

| | Whole population (n=123) | PCSK9i (n=83) | PCSK9i+ezetimibe (n=12) | PCSK9i+statin and ezetimibe (n=28) |
|-------------------------|-----------------------------|------------------|----------------------------|---------------------------------------|
| Responders, n (%) | 61 (49.6%) | 32 (38.6%) | 7 (58.3%) | 22 (78.6%) |
| Odds ratio | | | 2.20 | 6 |
| 95% Confidence interval | | | (0.6-8.1) | (2-17.6) |
| P value | | | 0.24 | 0.001 |

PCSK9i – proprotein convertase subtilisin/kexin type 9 inhibitors.

There were 61/123 (49.6%) responders in the study population, who achieved the target of at least 50% reduction in their LDL-c level from the baseline. They were 32/83 (38.6%) patients from the PCSK9i only group, 7/12 (58.3%) patients from the PCSK9i plus ezetimibe group, and 22/28 (78.6%) patients from the PCSK9i plus statin and ezetimibe group. Statistical analysis showed a positive statistically significant relationship between the PCSK9i plus statin and ezetimibe group and the responder rate (OR=6, CI [2-17.6], $P=0.001$) (Table 3), and a negative statistically significant relationship between the baseline LDL-c level and the responder rate (Odds ratio=0.46, CI [0.26-0.82], $P=0.009$).

Discussion

All FH patients are systematically classified as high cardiovascular risk patients according to the ESC guidelines for cardiovascular prevention [4]. A target of 70 mg/dl for LDL-c with at least 50% reduction from the baseline is recommended [4]. Recently, patients who could not achieve the target LDL-c value on statin and ezetimibe received the PCSK9i as triple combination therapy [4,16,17]. However, few reports reflected the application of PCSK9i in clinical practice, especially in FH patients. Here, we present a real-world, single-center experience of PCSK9i use in the FH population referred for lipoprotein apheresis.

In our study population, the use of PCSK9i was associated with a 49.1% reduction in LDL-c from the baseline. This result is similar to the 43% to 69% drop in LDL-c levels reported in previously published studies [18-26]. We found a potential synergic effect between the statin and PCSK9i, revealed through a statistically significant ($P<0.01$) reduction in the LDL-c levels observed in the patients taking PCSK9i on top of the statin, compared to the patients treated only with PCSK9i or with PCSK9i plus ezetimibe. A similar result was reported by Deshmukh et al, which showed no significant difference with the addition of ezetimibe [23]. Currently, there is no clear indication that the statin type or intensity relevantly affects the LDL-c lowering by PCSK9i. The 2019 ESC guidelines [4] and Ridker et al [17]

have endorsed a constant PCSK9i efficacy, regardless of the background therapy. Rallidis et al [27] reported a potent effect of PCSK9i on top of the statin in LDL-c reduction compared to those receiving PCSK9i monotherapy. By reducing the intracellular hepatic cholesterol, statin subsequently activates the sterol regulatory element binding protein transcription factor, increases not only the LDLR expression but also the PCSK9 expression, and consequently the circulating PCSK9 protein [5]. A 7.4% to 35% increase in the PCSK9 protein level was shown with the use of statins [28]. This boosts the efficacy of PCSK9i and facilitates the expected reduction in the LDL-c level. It explains the smaller reduction in LDL-c that is observed in patients treated with PCSK9i alone or combined with ezetimibe, making it more difficult to achieve the target goals in statin-intolerant patients. For this reason, the proportion of patients achieving the target 50% reduction in LDL-c from the baseline is 49.6% and it is lower than found in the literature (56% to 85.4%) [18-26]. Clinical trials have reported that 65% to 85% of the studied populations reach their treatment targets [29-31]. This discrepancy can be linked to the higher baseline LDL-c levels of our study population (277 mg/dl) compared to the previously described LDL-c levels in the literature (155 mg/dl to 219 mg/dl). The multivariate statistical analysis showed a statistically significant negative relationship between the baseline LDL-c levels and the potential satisfactory reduction in LDL-c levels ($P=0.009$); starting from a lower baseline, LDL-c is predicted to show a greater drop in LDL-c, and a significantly ($P=0.001$) higher proportion of responders are shown among those treated with statin and PCSK9i.

The recommended satisfactory reduction in the LDL-c levels in the present study's FH population were observed, while PCSK9i was associated with statin. In parallel, a low baseline LDL-c level is a predictor for a greater reduction in LDL-c, and no additional benefits were attributed to ezetimibe. Regardless of an overall observed alirocumab efficacy similar to the results of large randomized clinical trials, we highlight a statistically significant difference between the 2 prescribed regimens (with and without statin). It is important to consider that in our study, the treatment regimen excluding statin was prescribed in totally statin-intolerant patients.

To summarize, we emphasize the value of PCSK9i use in the FH population referred for lipoprotein apheresis in real-life practice, especially when combined with statin. Consequently, in order to obtain the best efficacy, PCSK9i is the appropriate therapy only in FH patients already on statin therapy and with moderate LDL-c levels before PCSK9i initiation.

Limitations

This study was a single-center experience reflecting the findings for PCSK9i use in a regional lipid clinic. Only alirocumab was used and its effects are reported in this study. The restricted inclusion criteria were defined according to the conditions for PCSK9i-reimbursement approval by the French health authorities. The 6-month follow-up is a short period to monitor the long-term LDL-c efficacy in FH patients.

Conclusions

We presented a single-center study showing an overall efficacy of PCSK9i in real life for the heterozygous FH population referred for lipoprotein apheresis. In these patients, the association of statin is essential for a greater reduction in LDL-c and an improved chance to achieve the target goals as a significant difference has been shown between PCSK9i monotherapy and the statin-associated regimen. Further research is needed to disentangle the best predictive parameters of PCSK9i efficacy in this severe FH population.

Department and Institution Where Work Was Done

Department of Cardiology, Toulouse-Rangueil University Hospital, Toulouse, France.

Conflict of Interest

The authors declare they have no conflict of interest. Prof. Jean Ferrières has received lecture fees from Amgen, MSD, Sanofi, and Servier.

Supplementary Data

Supplementary Online Table 1. Heterozygous mutated genes of the study participants.

Supplementary/raw data available from the corresponding author on request.

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