Original paper

Effectiveness and safety of proprotein convertase subtilisin/kexin type 9 inhibitors in patients with familial hypercholesterolemia. Our experience in implementing the drug program of the Polish National Health Fund

Beata Bobrowska[1], Agata Krawczyk-Ożóg[1,2], Stanisław Bartuś[1,3], Renata Rajtar-Salwa[1]

[1]Department of Cardiology and Cardiovascular Interventions, University Hospital, Krakow, Poland
[2]HEART – Heart Embryology and Anatomy Research Team, Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland
[3]2nd Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland

Adv Interv Cardiol 2022; 18, 2 (68): 162–166
DOI: https://doi.org/10.5114/aic.2022.118533

Abstract

Introduction: Heterozygous familial hypercholesterolemia (FH) is characterized by an elevated plasma low-density lipoprotein cholesterol (LDL-C) concentration despite intensive statin and ezetimibe therapy, which significantly increases the cardiovascular risk.

Aim: The study evaluated the efficacy and safety of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirocumab and evolocumab, in reducing lipids in patients with FH.

Material and methods: This was a single-center analysis of 22 patients diagnosed with FH treated with the PCSK9 inhibitors under the drug program of the National Health Fund. The follow-up interviews and laboratory tests were performed at baseline (22 patients), 3 months (22 patients) and 15 months (9 patients) after the first dose of PCSK9 inhibitors.

Results: The mean (SD) baseline level of the total LDL-C fraction was 4.7 ±1.6 mmol/l in the whole group of patients and was significantly reduced after 3 and 15 months of PCSK9 inhibitors therapy to 1.7 ±1.6 and 1.6 ±1.1 mmol/l, respectively. The average percentage of reduction in LDL-C level was 64.9 ±23.7% after 3 months and 66.9 ±18.4% after 15 months. In comparison with baseline, a significant reduction in total cholesterol was observed at both time points (p <0.0002). There were no adverse cardiovascular events or significant growth in the level of alanine transaminase, creatinine, and creatine kinase throughout the study.

Conclusions: Patients with FH treated with PCSK9 inhibitors achieved a significant reduction of LDL-C and total cholesterol with the safety of this treatment in follow-up.

Key words: proprotein convertase subtilisin/kexin type 9 inhibitors, alirocumab, evolocumab, heterozygous familial hypercholesterolemia.

Summary

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors offer a chance to treat hypercholesterolemia when widely available therapeutic strategies with statin and ezetimibe are insufficient to achieve recommended treatment goals. This was a single-center analysis of 22 patients diagnosed with familiar hypercholesterolemia (FH) treated with the PCSK9 inhibitors. These patients achieved a significant reduction of LDL-C and total cholesterol with the safety of this treatment in follow-up. PCSK9 inhibitors should be intensively implemented in patients with FH besides conventional treatment.

Introduction

Familial hypercholesterolemia (FH) leads to substantially increased low-density lipoprotein cholesterol (LDL-C) levels and a significantly increased risk of atherosclerosis and premature cardiovascular diseases. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is one of the main pathogenic FH genes, so an increasing number of studies have focused on finding effective therapeutic methods based on PCSK9 [1]. PCSK9 regulates the level of circulating LDL-C by enhancing the

Corresponding author:
Renata Rajtar-Salwa MD, PhD, Department of Cardiology and Cardiovascular Interventions, University Hospital, 2 Jakubowskiego St, 30-688 Krakow, Poland, phone/fax: +48 12 400 22 67, e-mail: rrajtar@su.krakow.pl
Received: 20.07.2022, **accepted:** 27.07.2022.

intracellular degradation of hepatic low-density lipoprotein receptors. A decreased level of low-density lipoprotein receptor causes growth of LDL-C concentration in plasma. Alirocumab and evolocumab are human monoclonal antibodies whose mechanism of action involves reduction of the plasma level of PCSK9. Thus, it will result in increased expression of hepatic low-density lipoprotein receptors at the cell surface and a reduction of serum LDL-C levels [2]. This pharmacotherapy is effective in all patients with hepatic low-density lipoprotein receptor expression as well as in people with heterozygous FH. Patients with homozygous FH without low-density lipoprotein receptors respond poorly to these medications [3, 4]. These drugs represent a chance to treat hypercholesterolemia when widely available therapeutic strategies with statin and ezetimibe are insufficient to achieve recommended treatment goals [4]. PCSK9 inhibitors are rarely used in Poland due to the high cost of this treatment and no refunds. The National Health Fund drug program provides a treatment opportunity to selected Polish patients with FH.

Aim

This study presents data on the efficacy and safety of PCSK9 inhibitors in patients with FH.

Material and methods

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Study population

The study group comprised 22 consecutive patients included in treatment with PCSK9 inhibitors from October 2019 to March 2022 at the University Hospital in Krakow, Poland. These patients had been diagnosed with FH and met the criteria for being included in the drug program of the National Health Fund. The criteria used for inclusion fulfilled the following conditions: (1) age 18 and over; (2) definite diagnosis of heterozygous FH, which means > 8 points on the Dutch Lipid Clinic Network (DLCN) scale; (3) fulfillment of the eligibility criteria for LDL-C apheresis treatment, and for patients already treated fulfillment of these criteria at the initiation of LDL-C apheresis treatment. Eligibility criteria for LDL-C apheresis were LDL-C > 160 mg/dl (4.1 mmol/dl) despite a low-fat diet and:

- Intensive treatment with maximum doses of statins used for 6 months (including combination therapy with ezetimibe for a minimum of 1 month). Maximum doses of statins in monotherapy means atorvastatin 80 mg or rosuvastatin 40 mg. Combination therapy means atorvastatin 40–80 mg or rosuvastatin 20–40 mg with ezetimibe 10 mg;
- Or intensive statin therapy with the maximum tolerated dose used for 6 months (including combination therapy with ezetimibe 10 mg for a minimum of 1 month).

The LDL-C cut-off point changed to > 100 mg/dl (2.5 mmol/dl) and the duration of statin therapy was shortened to 3 months, including 1 month of combination therapy with ezetimibe during the study.

Patients who fulfilled the above criteria were included in the study and were administered 150 mg of alirocumab or 140 mg of evolocumab subcutaneously every 2 weeks in combination with a low-fat diet and previously tolerated treatment with a combination of statin and ezetimibe.

The exclusion criteria are secondary causes of hypercholesterolemia, homozygous FH, glomerular filtration rate < 30 ml/min/1.73 m^2, chronic liver disease classified into Child-Pugh class C, pregnancy, breastfeeding and hypersensitivity to the drugs or a component of them. In addition, the development of severe allergic reactions after administration of the drug and lack of efficacy of treatment assessed after 3 months, defined as a reduction in LDL-C at < 30% relative to the baseline level, was a reason to exclude this patient from further treatment.

Data collection

The baseline clinical data were obtained from the patients' medical history and interviews. The presence of comorbidities, especially cardiac and peripheral interventions, aortic stenosis, atrial fibrillation, arterial hypertension, diabetes mellitus, peptic ulcer disease, thyroid disorders, previous cerebrovascular accidents and chronic kidney disease, was noted.

Blood samples were collected during patient inclusion. The levels of LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, alanine transaminase, creatine kinase and creatinine were measured. The follow-up interviews and laboratory tests were conducted during follow-up visits after 3 months (22 patients) and 15 months (9 patients) after the first dose of PCSK9 inhibitors.

Statistical analysis

Standard descriptive statistical methods were used to analyze the study data. The normality of the data was evaluated with the Shapiro-Wilk test. Continuous variables were presented as mean (standard deviation (SD)) and median (interquartile range (IQR)). Categorical variables were described as numbers and percentages. The Wilcoxon signed-rank test (for non-normally distributed data) or paired Student's *t*-test (for normally distributed data) was applied to assess changes in blood test results at time points of follow-up. *P*-values less than 0.05 were considered statistically significant. Statistica software, version 13 (StatSoft, Inc., Kraków, Poland) was used for all analyses.

Results

The mean age of included patients was 51.9 ±15.3 years. Men constituted 40.9% (9 patients) of the study

group. Among all patients, 7 (31.8%) had a history of at least one myocardial infarction, 11 (50.0%) patients underwent percutaneous cardiac intervention and 5 (22.7%) coronary artery bypass grafting. Four (18.2%) patients had a history of peripheral angioplasty. Four (18.2%) patients suffered from diabetes mellitus, 11 (50.0%) from arterial hypertension, 2 (9.1%) from atrial fibrillation, 3 (13.6%) had previous stroke, 4 (18.2%) had diagnosed thyroid disorders, 2 (9.1%) peptic ulcer disease, 3 (13.6%) chronic kidney disease but they had GFR > 30 ml/min/1.73 m^2, and 7 (31.8%) were active smokers or had quitted. Three (13.6%) had at least mild aortic stenosis in echocardiography. The median (IQR) score of the Dutch Lipid Clinic Network scale was 11 (9–16). Eight patients had a genetic test performed, which confirmed FH. In physical examination tendon xanthomas were found in 4 (18.2%) patients and xanthelasma palpebrarum in 3 (13.6%) patients, whereas no patients had an arcus cornealis at age < 45 years. All patients had normal TSH levels (the mean value 1.5 (0.7) µIU/ml (normal range: 0.27–4.2)). A combination of rosuvastatin 20–40 mg with ezetimibe 10 mg was used by 12 (54.5%) patients; atorvastatin 40–80 mg with ezetimibe 10 mg was used by 3 (13.6%) patients. Due to the intolerance of treatment with maximum doses, 1 (4.5%) patient was using atorvastatin 10 mg with ezetimibe 10 mg, 3 (13.6%) rosuvastatin 5–10 mg with ezetimibe 10 mg and 2 (9.1%) patients only ezetimibe 10 mg. Due to complete intolerance of statins and an allergic reaction to ezetimibe, 1 (4.5%) patient did not use either statin or ezetimibe.

The mean (SD) baseline level of LDL-C was 4.7 ±1.6 mmol/l in the whole group of patients and was reduced to 1.7 ±1.6 and 1.6 ±1.1 mmol/l after 3 and 15 months, respectively, after the first dose of PCSK9 inhibitors. The percentage reduction of LDL-C level was 64.9 ±23.7% after 3 months and 66.9 ±18.4% after 15 months. The average total cholesterol level in patients was 7.1 ±1.7 mmol/l at baseline. A significant reduction of total cholesterol compared to baseline was observed at both time points: 4.2 ±2.2 after 3 months and 4.0 ±1.5 after 15 months. All *p*-values of total cholesterol and LDL-C before versus successive time points were statistically significant (Table I). After 3 months of therapy 17 (77.3%) patients had LDL-C < 1.4 or < 1.8 mmol/l, as recommended by the guidelines. We did not observe a significant increase in the level of alanine transaminase, creatinine, or creatine kinase. Furthermore, we did not report any cardiovascular events during the follow-up period. Detailed data for all blood test results are listed in Table I.

In the study group 5 patients finished the therapy earlier: 1 patient refused to continue treatment after almost 12 months of therapy due to muscle and joint pain and 4 patients did not fulfill the criteria for continuation therapy after 3 months of treatment (LDL-C cholesterol decreased < 30%). The reason was the later genetic diagnosis of the variant of homozygous FH in 1 patient and probably discontinuation of baseline therapy (statin plus ezetimibe) in another.

Discussion

The analysis shows significant differences between the baseline values of LDL-C and total cholesterol compared to those obtained in successive follow-up periods.

In Poland, the prevalence of FH is 1 : 250 based on a meta-analysis of six observational studies of 136 300 adults [5–7]. In a very-high-risk Polish population, FH occurs much more often [8, 9]. In the studies mentioned above, the diagnosis of FH was established based on the phenotypic criteria and the DLCN algorithm but without

Table I. Results of blood laboratory tests. Mean±standard deviation and median (interquartile range) at baseline and during follow-up

Parameter	Baseline (*N* = 22)	3 months (*N* = 22)	*P*-value baseline vs. 3 months	15 months (*N* = 9)	*P*-value baseline vs. 15 months
Total cholesterol [mmol/l]	7.1 ±1.7 6.6 (6.0–7.9)	4.2 ±2.2 3.1 (2.6–5.4)	0.0002	4.0 ±1.5 4.1 (3.0–4.7)	0.0001
LDL [mmol/l]	4.7 ±1.6 4.3 (3.5–5.4)	1.7 ±1.6 1.1 (0.9–1.6)	0.00004	1.6 ±1.1 1.5 (0.7–2.2)	0.008
HDL [mmol/l]	1.4 ±0.5 1.2 (1.0–1.5)	1.4 ±0.5 1.3 (1.2–1.5)	0.42	1.5 ±0.5 1.5 (1.1–1.7)	0.14
Triglyceride [mmol/l]	2.6 ±3.0 1.5 (1.2–2.3)	2.7 ±5.4 1.3 (0.8–1.9)	0.02	2.8 ±4.0 1.5 (0.8–2.0)	0.68
Alanine transaminase [U/l]	28.5 ±13.5 23.0 (19.0–37.5)	34.4 ±30.6 23.0 (16.0–38.0)	0.30	44.4 ±47.5 27.5 (21.5–40.3)	0.58
Creatine kinase [U/l]	131.2 ±87.1 96.5 (80.3–154.3)	120.4 ±57.0 97.5 (76.0–152.8)	0.79	180.7 (82.5) 146.0 (138.0–221.0)	0.59
Creatinine [µmol/l]	77.0 ±21.6 73.0 (61.3–86.8)	86.5 ±34.4 78.6 (66.7–91.5)	0.86	82.6 ±17.0 83.2 (69.8–97.4)	0.48

N – number of samples, LDL-C – low-density lipoprotein, HDL – high-density lipoprotein.

determining the FH mutation due to the low availability and cost of genetic testing. There were alarming reports that FH is inadequately recognized and treated in Poland. Only 32.8% of patients with a DLCN score ≥ 6 received high statin doses. Other therapies, such as ezetimibe combined with statins or ezetimibe monotherapy, were used in a minority of patients [6]. The optimal lipid-lowering therapy is necessary to reduce the risk of cardiovascular events. Based on the results from many clinical trials, which were carried out on a wide range of patients, evolocumab and alirocumab were approved for treatment in 2015 [10]. In patients with heterozygous FH, evolocumab was well tolerated and caused a 60% decrease in LDL-C [11]. Also, alirocumab reduced LDL-C levels by approximately 40–60% in patients with this diagnosis [12, 13]. Additionally, the PCSK9 inhibitor plus high-intensity statin and plus ezetimibe could result in an average LDL-C reduction of about 85% [4]. The treatment with these two monoclonal antibodies reduced the risk of cardiovascular events [14, 15]. In large trials on PCSK9 inhibitors, clinical benefits occurred with lowering the plasma LDL-C levels more aggressively below current targets to approximately 20 mg/dl [16]. In our study, the mean (SD) LDL-C reduction after 3 months of therapy was 64.9 ±23.7% and after 15 months was 66.9 ±18.4%. Four (18.2%) patients showed a reduction in LDL-C of < 30%. Table II shows the LDL-C and total cholesterol reduction after 3 months of PCSK9 inhibitors with other lipid-lowering therapies.

In the literature, PCSK9 inhibitor therapy is safe, with no serious adverse effects. The most common side effect was injection-site reactions [16]. We observed muscle-re-

Table II. LDL-C and TC reduction after 3 months of PCSK9 inhibitors with other lipid-lowering therapies (mean ± SD)

Number of patients	Lipid-lowering therapy	Baseline LDL-C [mmol/l]	3 months LDL-C [mmol/l]	Reduction of LDL-C after 3 months (%)	Baseline TC [mmol/l]	3 months TC [mmol/l]	Reduction of TC after 3 months (%)
6	Rosuvastatin 40 mg Ezetimibe 10 mg Alirocumab	5.1 ±2.1	2.3 ±2.7	63.7 ±31.5	7.5 ±1.8	4.5 ±3.0	54.6 ±30.0
4	Rosuvastatin 40 mg Ezetimibe 10 mg Evolocumab	4.1 ±1.2	1.6 ±1.4	57.7 ±35.9	5.9 ±1.5	3.3 ±1.4	41.3 ± 27.3
1	Rosuvastatin 20 mg Ezetimibe 10 mg Alirocumab	7.1	1.3	81.7	9.8	4.8	51.0
1	Rosuvastatin 20 mg Ezetimibe 10 mg Evolocumab	4.2	1.7	59.5	6.2	4.0	35.5
1	Rosuvastatin 10 mg Ezetimibe 10 mg Alirocumab	3.4	0.9	73.5	5.0	2.5	50.0
1	Rosuvastatin 10 mg Ezetimibe 10 mg Evolocumab	2.9	1.0	65.2	5.6	2.9	56.1
1	Rosuvastatin 5 mg Ezetimibe 10 mg Alirocumab	6.3	0.5	89.6	4.8	1.9	69.8
1	Atorvastatin 40 mg Ezetimibe 10 mg evolocumab	4.2	1.1	73.6	5.9	3.1	47.5
1	Atorvastatin 80 mg Ezetimibe 10 mg Alirocumab	3.3	1.3	60.1	7.3	9.7	–32.9
1	Atorvastatin 80 mg Ezetimibe 10 mg Evolocumab	2.9	1.1	62.1	4.7	2.8	40.4
1	Atorvastatin 10 mg Ezetimibe 10 mg Alirocumab	5.2	1.30	75.0	9.8	5.4	44.9
2	Ezetimibe 10 mg Alirocumab	6.3 ±0.7	3.1 ±1.6	49.0 ±30.3	8.9 ±0.07	5.5 ±1.4	37.8 ±16.5
1	Alirocumab	5.4	1.30	75.9	7.70	3.8	50.7

LDL-C – low-density lipoprotein cholesterol, TC – total cholesterol.

lated adverse events in 1 patient after almost 12 months of alirocumab therapy. No side effects were observed in the remaining patients. In the FOURIER trial, the rate of muscle-related events was approximately 5%, while the rate of allergic reactions was 3.1% in the evolocumab group and did not differ significantly from the placebo group [17]. The ODYSSEY outcomes trial showed a general allergic reaction after alirocumab in 7.9% of patients and there was no significant difference from placebo groups [15]. Statin-associated muscle symptoms were reported in about 10–15% of individuals in observational studies [4]. In comparison, in blinded randomized trials of statins versus placebo, muscle symptoms were not so common [18, 19].

In our group of patients, 10 (45.5%) patients used rosuvastatin 40 mg with ezetimibe 10 mg, and 2 (9.1%) used a combination of atorvastatin 80 mg with ezetimibe 10 mg. The PCSK9 inhibitor therapy was essential for patients with FH who cannot tolerate maximum doses of statin and ezetimibe, as it gives a chance to approach the therapeutic goal of LDL-C.

There were some limitations of the study. First, this was a single-center study, and therefore there was a small sample size relating to a limited number of patients with FH and the difficult conditions to receive the treatment refunds. The 15-month follow-up was unavailable in all patients because some were treated in this program for a shorter time. Nevertheless, we present preliminary results and believe that this study will increase PCSK9 inhibitors' popularity as a new line of effective treatment of FH.

Conclusions

In patients with FH PCSK9 inhibitors reduced LDL-C by about 65% during follow-up. Four (18.2%) patients did not achieve an LDL-C reduction > 30%. There were no adverse cardiovascular events throughout the observation period as well as an increase in the levels of creatine kinase, alanine transaminase and creatinine. These new therapeutic options should be intensively implemented in patients with FH besides conventional treatment.

Acknowledgments

Beata Bobrowska and Agata Krawczyk-Ożóg – equal contribution.

Conflict of interest

The authors declare no conflict of interest.

References

1. Guo Q, Feng X, Zhou Y. PCSK9 variants in familial hypercholesterolemia: a comprehensive synopsis. Front Genet 2020; 11: 1020.
2. Norata GD, Tibolla G, Catapano AL. Targeting PCSK9 for hypercholesterolemia. Annu Rev Pharmacol Toxicol 2014; 54: 273-93.
3. Blom DJ, Blanchard V, Chemello K, et al. HHS Public Access 2019; 38: 592-8.
4. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41: 111-88.
5. Vallejo-Vaz AJ, Marco M De, Stevens CAT, et al. Overview of the current status of familial hypercholesterolaemia care in over 60 countries – The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Atherosclerosis 2018; 277: 234-55.
6. Chlebus K, Cybulska B, Gruchała M, et al. Prevalence, diagnosis, and treatment of familial hypercholesterolaemia in outpatient practices in Poland. Kardiol Pol 2018; 76: 960-7.
7. Pajak A, Szafraniec K, Polak M, et al. Prevalence of familial hypercholesterolemia: a meta-analysis of six large, observational, population-based studies in Poland. Arch Med Sci 2016; 12: 687-96.
8. Bobrowska B, Zasada W, Rajtar-Salwa R, et al. Prevalence of familial hypercholesterolemia in patients with acute coronary syndromes. Kardiol Pol 2019; 77: 475-7.
9. DyrbuśK, Gąsior M, Desperak P, et al. The prevalence and management of familial hypercholesterolemia in patients with acute coronary syndrome in the Polish tertiary centre: results from the TERCET registry with 19,781 individuals. Atherosclerosis 2019; 288: 33-41.
10. Catapano AL, Pirillo A, Norata GD. New pharmacological approaches to target PCSK9. Curr Atheroscler Rep 2020; 22: 24.
11. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015; 385: 331-40.
12. Ginsberg HN, Rader DJ, Raal FJ, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. Cardiovasc Drugs Ther 2016; 30: 473-83.
13. Kastelein JJP, Ginsberg HN, Langslet G, et al. ODYSSEY FH i and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015; 36: 2996-3003.
14. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376: 1713-22.
15. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018; 379: 2097-107.
16. Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. Nat Rev Cardiol 2019; 16: 155-65.
17. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376: 1713-22.
18. Finegold JA, Manisty CH, Goldacre B, et al. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. Eur J Prev Cardiol 2014; 21: 464-74.
19. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circ Cardiovasc Qual Outcomes 2013; 6: 390-9.