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Real-world use of PCSK9 inhibitors: A single-center experience

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Abstract

Objective: Hyperlipidemia is an important risk factor for atherosclerotic cardiovascular disease. Many patients are intolerant to or have limited benefit from statins. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been approved for treating hyperlipidemia in these patients. We sought to investigate the impact of these medications in a real-world cardiology practice.

Methods: This was a retrospective study of 17 patients with either heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease with low-density lipoprotein cholesterol (LDL-C) levels above the treatment target despite maximally tolerated statins. Baseline lipid profile was compared with a repeat lipid profile obtained 4 to 6 weeks after initiating treatment with a PCSK9 inhibitor.

Results: The average duration of PCSK9 inhibitor treatment was 10.7 months. Lipid profile comparison showed that total cholesterol decreased from 243 ± 72 to 148 ± 39 (mg/dL) (39% reduction), triglycerides decreased from 185 ± 86 to 149 ± 62 (mg/dL) (19.5% reduction), high-density lipoprotein cholesterol increased from 56 ± 20 to 62 ± 26 (mg/dL) (10.7% increase), and LDL-C decreased from 154 ± 30 to 57 ± 32 (mg/dL) (63% reduction) from baseline.

Conclusions: PCSK9 inhibitors as add-on therapy to maximally tolerated statins resulted in an approximately 63% reduction in LDL-C.

Keywords

Dyslipidemia, statin, PCSK9 inhibitor, LDL cholesterol, atherosclerotic cardiovascular disease, lipid-lowering therapy

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Introduction

Hyperlipidemia is a well-known risk factor for the development of atherosclerotic cardiovascular disease (ASCVD).[1] Statin therapy is the standard treatment for people with or at high risk for ASCVD according to American College of Cardiology (ACC) and American Heart Association (AHA) guidelines.[2] However, there are limited treatment options for patients who are either intolerant to statins or do not achieve their low-density lipoprotein cholesterol (LDL-C) goals despite receiving maximally tolerated statin therapy.

Ezetimibe is recommended as second-line therapy for patients in this group,[2] and can offer additional LDL-C reduction, although the percentage of patients achieving the LDL-C target level by adding ezetimibe is relatively low.[3]

Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) have emerged as a new class of drugs that effectively lower LDL-C levels. The Food and Drug Administration (FDA) has approved two PCSK9 inhibitors for LDL-C reduction: evolocumab and alirocumab. These medications reduce the degradation of LDL-C receptors in hepatocytes by inhibiting PCSK9, leading to an increased number of receptors and decreased circulating LDL-C levels.[4,5]

The FOURIER trial was the first published outcome trial to show a significant cardiovascular benefit of PCSK9 inhibitors when used concomitantly with statins. It also showed that the use of evolocumab on a background of statin therapy lowered LDL-C levels to a median of 30 mg/dL (59% reduction), reduced the risk of primary composite endpoints of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization by 15% ($p<0.001$), and the composite endpoints of cardiovascular death, myocardial infarction, or stroke by 20% over a mean of 2.2 years follow-up.[6] Furthermore, the ODYSSEY outcome study (American College of Cardiology 2018 Annual Scientific Session, Orlando, FL) showed that the use of alirocumab in patients with acute coronary syndrome resulted in a 54.7% reduction in LDL to a mean of 53 mg/dL at 48 months, and significantly reduced the rate of major adverse cardiovascular events including death, myocardial infarction, unstable angina, and stroke from 11.1% to 9.5% ($p=0.0003$).

However, the applicability of the findings from these outcome trials to real-world patients remains unclear. We therefore conducted a retrospective study to examine the effect of PCSK9 inhibitors on lipid levels in patients attending a community practice and to compare it with the results obtained from previous outcome trials.

Methods

Patients

In our practice, patients are treated to achieve target LDL-C levels based on 2015 National Lipid Association (NLA) Guidelines.[7] The NLA has recommended specific LDL-C goals based on clinical risk factors such as diabetes mellitus (DM), chronic kidney disease (CKD), and established coronary artery disease (CAD). Goals are defined according to the number of ASCVD risk factors: low-risk patients with 0 to 1 risk factors should start drug therapy when LDL-C ≥ 160 mg/dL with an LDL-C goal of < 100 mg/dL; moderate-risk patients with 2 risk factors should start drug therapy when LDL-C ≥ 130 mg/dL with an LDL-C goal of < 100 mg/dL; high-risk patients with ≥ 3 risk factors, diabetic patients with 0 to 1 other major ASCVD risk factors and without end-organ damage, CKD stage IIIb, or severe hypercholesterolemia (e.g., heterozygous familial hypercholesterolemia

(HeFH) with LDL-C > 190 mg/dL) should start drug therapy when LDL-C ≥ 100 mg/dL with an LDL-C goal <100 mg/dL; and very high-risk patients with established ASCVD, or DM with ≥2 major ASCVD risk factors or evidence of end-organ damage, should start drug therapy when LDL-C ≥ 70 mg/dL with an LDL-C goal < 70 mg/dL.

All patients provided verbal informed consent to participate in this community-based practice research study. The manuscript was written in compliance with the Equator Network Guidelines for observational studies.

Treatment and follow-up

This was a retrospective study of data from 17 patients with an FDA-approved on-label indication for PCSK9 inhibitors, having either familial hypercholesterolemia or established ASCVD with hyperlipidemia above target LDL-C levels on maximum tolerated statins with or without ezetimibe. All patients had prior authorization for insurance reimbursement and received treatment with a PCSK9 inhibitor without interruption during the study follow-up period. Baseline characteristics were reviewed, and compliance was confirmed during follow-up visits and via a periodic lipid profile check.

The maximum tolerated dose of statin was defined as the highest dose of statin therapy which could not be further titrated up because of side effects, or the maximum recommended dose. Statin intolerance was defined as intolerance to at least three different statins, manifesting as side effects including muscle aches and elevated liver enzyme levels. Baseline lipid profiles prior to PCSK9 inhibitor therapy were compared with profiles obtained 4 to 6 weeks after initiation of therapy.

Results

A cohort of 17 patients who met the FDA on-label indication for PCSK9 inhibitors were included in the study. The mean age of patients was 63.11 ± 8.3 years, and the percentage of males and females as 41.1% and 58.9%, respectively. One patient (5.9%) had HeFH and qualified for primary prevention. The other 16 patients had established ATCVD (94.1%) and qualified for secondary prevention. The prevalence of established CAD was 82.3%, cerebrovascular accident was 11.8%, and peripheral vascular disease was 11.8%. Furthermore, 70.6% of the study cohort had hypertension, 17.6% had DM, 17.6% had carotid artery disease as evidenced by duplex or carotid angiogram, and 23.5% had CKD (Table 1).

Six patients (35.3%) were intolerant to statins, having developed side effects requiring the discontinuation of therapy. Eleven patients (64.7%) were on the maximum tolerated statin dose (3 patients, atorvastatin 80 mg/d; 2 patients, atorvastatin 40 mg/d; 1 patient, pravastatin 80 mg/d; 2 patients, rosuvastatin 20 mg/d; and 3 patients, rosuvastatin 40 mg/d). Three patients (17.6%) were on ezetimibe 10 mg/day.

The baseline lipid profile of the study cohort included total cholesterol level of 243 ± 72 mg/dL, triglycerides 185 ± 86 mg/dL, high-density lipoprotein cholesterol (HDL-C) 56 ± 21 mg/dL, and LDL-C 155 ± 31 mg/dL. The average duration of treatment with PCSK9 inhibitors was 2 to 17 months (mean of 10.7 months).

Table 1. Baseline patient characteristics

Age (years)	63 ± 8.3
Female sex (%)	58.9
Coronary artery disease (%)	82.3
Cerebrovascular accident (%)	11.8
Peripheral vascular disease (%)	11.8
Hypertension (%)	70.6
Diabetes mellitus (%)	17.6
Carotid artery disease (%)	17.6
Chronic kidney disease (%)	23.5

Lipid values changed significantly following initiation of PCSK9 inhibitor therapy. Total cholesterol decreased to 148 ± 39 mg/dL for a total percent reduction of 39%, triglycerides decreased to 149 ± 62 mg/dL (reduction of 19.5%), HDL-C increased to 62 ± 26 mg/dL (increase of 10.7%), and LDL-C decreased to 57 ± 32 mg/dL (reduction of 63%) from baseline values (Table 2).

One out of 17 patients (5.8%) developed an injection site reaction (redness) which resolved spontaneously without the need to discontinue the medication. No other side effects were observed in our study cohort.

Discussion

The management of LDL-C plays a role in both the primary and secondary prevention of ASCVD. The likelihood of ASCVD events and mortality decreases with the reduction in LDL-C level in patients with and without established ASCVD.[8] Most therapies that lower LDL-C lead to lower rates of myocardial infarctions and strokes, although it has been more difficult to demonstrate a mortality benefit of treatment with these medications. Statins have shown an improvement in survival when compared with placebo.[9,10] However, high-intensity statin therapy did not reduce mortality in comparison with moderate-intensity statins in patients with non-acute coronary syndrome.[11] Statin therapy combined with ezetimibe also failed to produce a mortality benefit.[12] Similar results were reported in the FOURIER trial of the PCSK9-inhibitor, evolucumab, in that no decrease in cardiovascular or all-cause mortality was observed.[6] Nevertheless, multiple studies have established that the lowering of LDL-C, regardless of the agent utilized, leads to a reduction in risk of the composite endpoint of major adverse cardiovascular events.

2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce ASCVD risk in adults focused on four groups that would benefit from the lipid-lowering effects of statin therapy: patients with clinical ASCVD, LDL-C levels $\geq$190 mg/dL, DM, and a 10-year ASCVD risk of $\geq$7.5%. Statin therapy was to be initiated at moderate- to high-intensity doses to reduce LDL-C levels by 30% to 50% or $\geq$50%.[13] The IMPROVE-IT was still ongoing trial at the time that these guidelines were published, and PCSK9-inhibitors were under development. In 2016, the ACC released an expert consensus decision pathway for non-statin therapies for lowering LDL-C. LDL-C goals still consisted of percentage reductions, but now allowed for optional target levels. In certain patient populations, LDL-C target levels of $<$70 or $<$100 mg/dL were considered. Ezetimibe and PCSK9-inhibitors were added as optional therapy if LDL-C goals were not met on maximally tolerated statin therapy alone.[14]

PSCK9 inhibitors have demonstrated a reduction in LDL-C in a dose-dependent pattern by as much as 60% in statin-intolerant patients, while a reduction in

Table 2. Effect of PCSK9 on lipid profile from baseline

Lipid component	Baseline	PCSK9 inhibitors	Change from baseline
Total cholesterol (mg/dL)	243 ± 72	148 ± 39	−39.1%
Triglycerides (mg/dL)	185 ± 86	149 ± 62	−19.5%
HDL-C (mg/dL)	56 ± 21	62 ± 26	+10.7%
LDL-C (mg/dL)	155 ± 31	57 ± 32	−63.2%

PCSK9, proprotein convertase subtilisin/kexin type 9; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

LDL-C of over 70% has been reported in patients already receiving statin therapy.[15] In addition to decreasing LDL-C, these agents may reduce triglyceride levels by 12% to 31% and increase HDL by 5% to 9%.[16] These encouraging findings have all been reported in randomized, controlled trials, meaning that the effect of PSCK9 inhibition on cholesterol levels in real-world clinical practice remains underreported. The significant alterations in LDL-C, HDL-C, and triglyceride levels observed in the present study are consistent with the findings reported in large clinical trials. Specifically, LDL-C and triglyceride levels in the present study were lowered to approximately 60% and 20%, respectively, which are comparable to the changes noted in previous trials. HDL-C increased by approximately 11%, a slightly larger effect than was found previously, and total cholesterol also declined by 39% in our patient population.

In our clinical practice, we aimed to treat patients with hyperlipidemia to reach a target level of LDL-C in accordance with the most recent NLA guidelines. We found that maximally tolerated statin therapy was not always effective in achieving these targets, despite the implementation of aggressive treatment strategies such as diet, exercise, and lipid-lowering agents. The addition of a PCSK9 inhibitor for specific patients resulted in a significant improvement in lipid profile. Target LDL-C goals of <70 and <100 mg/dL appear to be attainable with concomitant statin and PCSK9 inhibitor therapy. Given the findings of our study and the established evidence in support of their effect on lipid levels and cardiovascular outcomes, we plan to continue prescribing PCSK9 inhibitors for the attainment of target LDL-C goals in both primary and secondary prevention of ASCVD.

In conclusion, the use of PCSK9 inhibitors in clinical practice as add-on therapy to maximally tolerated statins resulted in 63% reduction in LDL cholesterol levels.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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