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Original Article

A safety and clinical efficacy analysis of PCSK9 monoclonal antibodies in patients with markedly elevated creatine phosphokinase levels

Ina Volis[1], Eric Hislop[2], Walid Saliba[2,3], Barak Zafrir[2,4]

[1]Department of Internal Medicine, Rambam Medical Center, Haifa, Israel; [2]Faculty of Medicine, Technion, Israel Institute of Medicine, Haifa, Israel; [3]Department of Community Medicine and Epidemiology, Lady Davis Carmel Medical Center, Haifa, Israel; [4]Department of Cardiology, Lady Davis Carmel Medical Center, Haifa, Israel

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Abstract: Introduction: PCSK9 inhibitors (PCSK9i) are often used in statin-intolerant patients, aiming to reduce low-density lipoprotein cholesterol (LDL-C). Along with the growing experience with their use, there is a lack of evidence regarding the safety, tolerability, and clinical utility of PCSK9i in patients with markedly elevated creatine phosphokinase (CPK) levels. Methods: We screened a comprehensive HMO database for patients treated with PCSK9i (Jan 2016-Dec 2019), in whom elevated CPK levels (>1,000 U/L) were documented prior to the initiation of therapy. Treatment plans, adherence, and the levels of CPK and LDL-C were analyzed. Results: Of the 1,600 patients initiating treatment with PCSK9i, 26 had prior CPK values >1,000 U/L [median (IQR): 3,687 (1,876-8,344) U/L]. All 26 patients were previously treated with statins, which presumably resulted in adverse effects (myalgia in 24, and rhabdomyolysis in 5 patients) therefore mandating their discontinuation. Concomitant secondary factors for CPK elevation were present in 11 patients, and included renal failure, rheumatoid disorders, hypothyroidism, intensive exercise, proteinuria and genetic muscular disease. Of the 26 patients treated with PCSK9i, alirocumab was administered to 12 patients, and evolocumab to 14. Following the initiation of treatment with either drug, 24 patients (92%) demonstrated a reduction in CPK of >50%, and in 12 (46%) CPK levels have returned to normal values. With regard to treatment goals, 17 patients (65%) have achieved an LDL-C level of <70 mg/dL, and 12 (46%) have reached a level of <55 mg/dL. No serious adverse reactions were documented, and only 2 patients discontinued the treatment (not due to muscle symptoms or CPK elevation). Conclusions: PCSK9i constitute a safe, tolerable, and effective treatment for hyperlipidemia in patients with markedly elevated CPK. While statin intolerance is a major cause for CPK elevation, concomitant etiologies for increased CPK values were rather common.

Keywords: Hypercholesterolemia, PCSK9 inhibitor, alirocumab, evolocumab, creatine phosphokinase, statin intolerance

Introduction

The PCSK9 (proprotein convertase subtilisin/kexin type 9) monoclonal antibodies, alirocumab and evolocumab, effectively reduce low-density lipoprotein cholesterol (LDL-C) and improve cardiovascular outcomes when added on top of statin therapy in patients with atherosclerotic cardiovascular disease (ASCVD) [1, 2]. However, patients with significantly elevated creatine phosphokinase (CPK) levels were excluded from large randomized controlled trials which evaluated the effect of PCSK9 inhibitors (PCSK9i) on cardiovascular outcomes: patients with CPK levels >3× upper limit of normal range (ULN) were excluded from the Odyssey Outcomes trial, and patients with CPK >5× ULN were excluded from the Fourier trial [1, 2]. While these pivotal trials did not evaluate the effects of PCSK9i among patients with elevated CPK, other studies that addressed the safety and tolerability of PCSK9i in cohorts of statin-intolerant patients [3] did not systematically followed CPK levels of the patients. In these studies, statin intolerance was most commonly referred to as an inability to tolerate several types or doses of statins, mostly by means of muscle symptoms; and while PCSK9i

were found to be safe and well tolerated, baseline CPK levels were not documented, or led to exclusion in cases where it was significantly elevated [4-8].

Notably, randomized controlled trials that studied the effect of PCSK9i found no increase in CPK levels, relative to the placebo group [9]. Nevertheless, there is little data regarding PCSK9i administration in patients with an a-priori elevated CPK [10, 11]. In light of this knowledge gap, and since lipid-lowering management of patients with very high CPK values is challenging due to limited treatment options [12], our current aim was to investigate the safety and clinical efficacy of PCSK9 monoclonal antibodies, in real-world hypercholesterolemic patients with markedly elevated CPK levels.

Methods

Patient population

This study is part of a retrospective cohort analysis of patients (n=1,600) initiating treatment with PCSK9 monoclonal antibodies (alirocumab or evolocumab) between January 2016 and December 2019 in Clalit Health Services (CHS), the largest health maintenance organization (HMO) in Israel [13]. Included in the current analysis were patients who have initiated PCSK9i therapy due to significant elevation of CPK levels (>1,000 U/L) which prevented therapeutic management of hyperlipidemia by statins. There were no exclusion criteria. The index date for each patient was defined as the first PCSK9i prescription fill. Cohort participants, for whom we had full access to patients' electronic data, were followed-up until discontinuation of PCSK9i treatment, or the end of the study period in June 2020. The patients' treatment plans, adherence, CPK and LDL-C levels with PCSK9i treatment were analyzed. The study was approved by CHS Ethics Committee (approval number 0139-19-COM2), in accordance with the Declaration of Helsinki, with waiving of the need for individual patient consent due to the retrospective design of the study.

Study variables

Demographic data, clinical variables, laboratory values, risk factors and comorbidities were retrieved from computerized database of CHS. Baseline lipid-lowering therapies were recorded during a six-month period prior to the index date. The different types of statins prescribed in each patient's history were documented, as were lipid-lowering drugs after the initiation of PCSK9i. LDL-C levels were recorded at 3 timepoints: (a) the peak level in the patients' history, (b) the pre-PCSK9i level, defined as the highest level measured in the year prior to the initiation of PCSK9i, and (c) most-recent (updated) lipid profile after initiation of PCSK9i. CPK levels and liver function tests were documented at 2 timepoints: (a) the peak level prior to initiation of PCSK9i, and (b) most-recent level under the treatment of PCSK9i. We searched each patient's electronic files for secondary predisposing and/or precipitating factors contributing to baseline CPK elevation. Study indicators included: (a) precipitating factors contributing to CPK elevation, (b) CPK reduction rates with PCSK9i treatment (>50% and return to normal range), (c) discontinuation rates of PCSK9i and their etiologies and (d) attainment rates of lipid goals under PCSK9 inhibition.

Statistical analysis

Categorical variables are reported as number and percentage, and continuous data are reported as mean and standard deviation, or median and interquartile range (IQR). Adherence and persistence to PCSK9i treatment was evaluated by analyzing medication discontinuation, defined as a gap of 60 days or more between the last day's supply of one prescription and the start of the next prescription. Attainment of LDL-C treatment goals after initiation of PCSK9i was assessed according to risk categories recommended by the European Society of Cardiology (ESC) 2019 dyslipidemia guidelines [14]. SPSS statistical software version 25.0 and MEDCALC version 16.8 were used to perform statistical analyses.

Results

A total of 1,600 patients insured by CHS initiated treatment with PCSK9i during the study period. Of them, 26 patients had elevated CPK levels above 1,000 U/L prior to the first prescription of PCSK9i, constituting the current study population. Mean age of the patients was 62±10 years (range 43-82) and 35% were women. Patients' baseline characteristics are presented in **Table 1**. ASCVD was evident in

Table 1. Patients' baseline characteristics

Variable	Patients treated by PCSK9 inhibitors Due to CPK >1000 U/L (n=26 patients)
Age (years)	62±10
Gender (Male)	17 (65%)
Ethnicity (Arabs)	4 (15%)
Socioeconomic status	
Low	8 (30.8%)
Middle	9 (34.6%)
High	9 (34.6%)
Obesity (body mass index ≥30 kg/m^2)	6 (23%)
Hypertension	12 (46%)
Diabetes	12 (46%)
Ever smoking	12 (46%)
Ischemic Heart Disease	15 (58%)
Prior Myocardial infarction	8 (31%)
Prior Stroke	1 (4%)
Peripheral Vascular Disease	1 (4%)
Carotid Artery Disease	3 (12%)
Atherosclerotic cardiovascular disease	17 (65%)
Laboratory values	
Pretreatment levels	
Aspartate aminotransferase (U/L)	67 (37-125)
Alanine aminotransferase (U/L)	50 (36-98)
Creatinine (mg/dL)	1.01 (0.84-1.28)
Bilirubin (mg/dL)	0.68 (0.47-1.15)
LDL-C (mg/dL)	126 (111-170)
Peak levels	
Thyroid stimulating hormone (IU/L)	2.6 (2.2-5.7)
CPK (U/L)	3687 (1876-8344)
LDL-C (mg/dL)	206 (190-228)
Most-recent levels	
CPK (U/L)	318 (79-524)
LDL-C (mg/dL)	57 (35-76)
HDL-C (mg/dL)	46 (39-55)

Data presented as number (%) and median (IQR), or ± standard deviation. CPK, creatinine posphokinase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Conversion factor ×0.0259 from mg/dL to mmol/L for LDL-C, HDL-C and total cholesterol, and ×0.0113 for triglyceride levels.

65% of the patients. Mean peak LDL-C in patients' history was 210±54 mg/dL and 19 patients (73%) had a baseline LDL-C level of >190 mg/dL.

All 26 patients were previously treated by statins. In 18 patients, ≥3 different statin types were prescribed. Myalgia was reported by most patients (n=24), and rhabdomyolysis was clinically diagnosed in 5. Abnormal liver function tests were noted in 8 out of the 26 patients. Peak measured CPK levels were 1,050-53,540 U/L [median (IQR): 3,687 (1,876-8,344)]. Concomitant secondary precipitating factors for CPK elevation were present in 11 patients, and included renal failure (n=5), inflammatory rheumatoid disorders (n=3), severe hypothyroidism (n=3), intensive exercise (n=2), nephrotic range proteinuria (n=1), and genetic muscular disease (n=1).

Treatment with evolocumab 140 mg was initiated in 14 patients, low-dose alirocumab (75 mg) in 10, and high-dose alirocumab (150 mg) in 2 patients. In 5 of the patients Ezetimibe was combined with a PCSK9i.

In 24 patients (92%) CPK reduction of >50% from peak levels was evident, and in 12 patients (46%) CPK values returned to normal range (**Figure 1**). During a median follow-up period of 20 months (IQR 13-32 months), 8 patients discontinued PCSK9i therapy: out of them, 6 reinitiated drug treatment after more than 60 days from the last prescription fill. Of the 2 cases in which the patients have indefinitely ceased PCSK9i treatment, none was in consequence of muscle symptoms. Rather, 1 patient terminated the treatment because of recurrent diarrhea, while the other did so due to lack of improvement of his hypertriglyceridemia. With PCSK9i treatment, 17 patients (65%) achieved LDL-C levels <70 mg/dL and 12 patients (46%) achieved LDL-C <55 mg/dL.

Discussion

Statin-associated muscle symptoms (SAMS) are the primary reason for statin intolerance, leading to treatment nonadherence, which may contribute to adverse clinical outcomes [12]. While SAMS are usually associated with normal or slightly elevated CPK values, myositis is defined as muscle symptoms in association with a substantially elevated serum CPK levels,

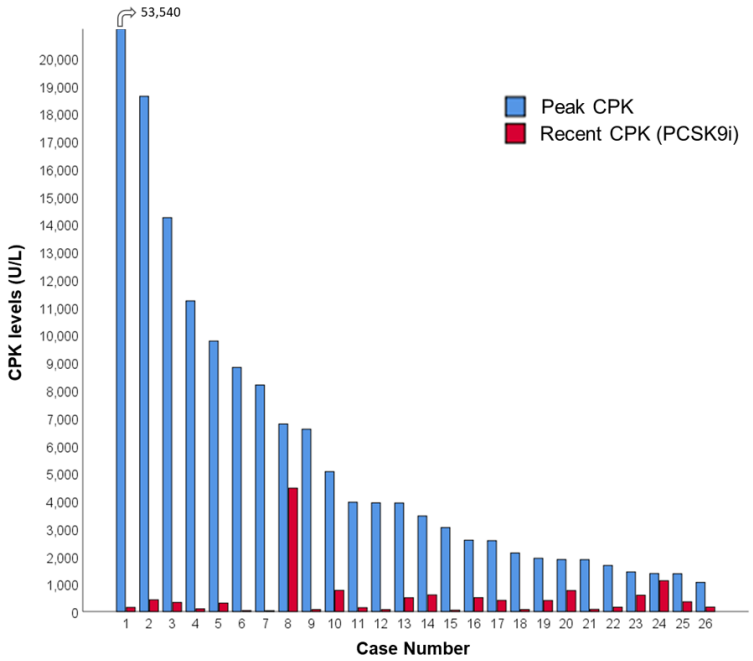

Figure 1. Creatine phosphokinase concentration: peak levels versus values under PCSK9 monoclonal antibodies. CPK, creatine posphokinase.

and is relatively uncommon [15]. Although elevated serum CPK levels may be a marker of inflammation and degeneration of the muscle tissue, in some cases CPK elevation is asymptomatic and is often without clear clinical significance. Consensus expert panels recommend temporary suspension of statin treatment in patients with muscle symptoms and elevated serum CPK levels >4× ULN. Therapy should be ceased in patients with CPK >10× ULN due to the potential risk for rhabdomyolysis [12, 15]. In patients with rhabdomyolysis or markedly elevated CPK levels, inherited and acquired precipitating factors should be sought after. These may include exertional physical activity, alcohol, drugs and toxins, sepsis, autoimmune diseases, and metabolic, endocrine or electrolyte disturbances. Additionally, in cases of recurrent rhabdomyolysis or persistent CPK elevation - inherited metabolic, mitochondrial and neuromuscular disorders should be ruled out [16]. Our results show that in nearly half of the patients with markedly elevated CPK levels, a concomitant precipitating factor for CPK elevation was present, alongside statin therapy. These findings emphasize the importance of identification of risk factors for myalgia and CPK elevation in patients receiving lipid lowering therapies, as well as tailoring treatment and follow up regimens individually.

It should be noted that studies investigating PCSK9 monoclonal antibodies in statin-intolerant patients, often did not provide informative data as for the management of those with markedly elevated CPK. The definition of statin-intolerance, by itself, does not refer to CPK values, but rather to clinical intolerance [4-8]. One study that did refer to patients as statin-intolerant not only by means of SAMS was the GAUSS-3 randomized trial that compared evolocumab versus ezetimibe in patients with muscle-related statin Intolerance [17]. In this study, only 19 (out of 218) patients were defined as statin-intolerant solely on the basis of their CPK levels (≥10× ULN). However, while these patients were considered eligible for the study, further follow-up did not distinguish them from the 199 patients that were included in the study based on SAMS, and they were not monitored separately any further. The GAUSS-3 trial reported that myalgia was evident in 21.9% of patients receiving ezetimibe versus 13.8% of those receiving evolocumab, whereas an increase in CPK was reported in only 1.2% and 2.4% of patients receiving ezetimibe or evolocumab, respectively [17]. Importantly, the extent to which CPK was increased following either treatment, and whether such increase occurred more often in patients with markedly elevated baseline CPK, were not reported. As the patients included in this study based on elevated CPK levels were not analyzed separately, little conclusions can be drawn specifically regarding this population.

In light of the scarcity of existing data regarding the subpopulation of patients with elevated CPK, the current analysis adds important real-world clinical information regarding the safety, tolerability, and efficacy of PCSK9i in such patients. Despite the limitation imposed by the size of the cohort, our results demon-

strate good adherence to PCSK9i therapy, with little concern for an increase or re-elevation of CPK levels under treatment, and with an impressive lipid management efficacy.

Conclusions

The study results support the safe and effective usage of PCSK9 monoclonal antibodies in high-risk, statin-intolerant patients with markedly elevated CPK levels. Our findings also underscore the need to actively seek for concomitant precipitating factors that may contribute to CPK elevation in patients receiving statin therapy.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Barak Zafrir, Cardiovascular Department, Lady Davis Carmel Medical Center, 7 Michal St., Haifa, Israel. Tel: +972-48250801/916; Fax: +972-48250801/916; E-mail: barakzmd@gmail.com

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