Research article

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PCSK9 inhibitors: The breakthrough lipid-lowering treatment at real-life setting
A 2-year regional lipid clinic experience

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ABSTRACT

Aim: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been demonstrated to be safe and effective in low-density lipoprotein cholesterol (LDL-C) lowering and cardiovascular risk reduction. Data on clinical implementation of PCSK9 inhibitors in real life setting in Greece is limited. Thus, we report 2-year experience with PCSK9 inhibitors in clinical practice at a University Hospital Lipid Clinic. **Patients and methods:** This is a retrospective study of patients who were first prescribed a PCSK9 inhibitor during 2016-2018. Patients had either established cardiovascular disease (CVD) and/or familial hypercholesterolemia (FH) and LDL-C level >100 mg/dL despite maximum tolerated high-intensity statin plus ezetimibe. Patient demographics, medical history, concomitant medications and laboratory results were documented during visits. **Results:** We included 37 patients (mean age 52 years, 56.8% males). Of patients, 28 (76%) had established CVD and 27 patients (74%) had FH. Concerning treatment, 33 patients (89%) were receiving high-intensity statin, while 35 patients (95%) were also on ezetimibe 10 mg. Addition of PCSK9 inhibitors (51% on evolocumab 140 mg per 2 weeks (Q2W), 22% on alirocumab 75 mg Q2W and 27% on alirocumab 150 mg Q2W) resulted in a reduction of total cholesterol by 42% and LDL-C by 59% after 2 months ($p<0.05$). These reductions remained unchanged after 1 and 2 years on treatment. Thirty patients (81%) achieved LDL-C treatment goal following PCSK9i treatment. Four patients (11%) developed minor adverse effects. No treatment discontinuation was reported. **Conclusion:** In real-life setting addition of PCSK9 inhibitors to maximally tolerated lipid-lowering therapy resulted in reductions of LDL-C levels of the magnitude seen in clinical studies. These reductions were sustainable during a 2-year follow-up.

KEY WORDS: *PCSK9 inhibitors, dyslipidemia, familial hypercholesterolemia, statins, cardiovascular disease, ezetimibe*

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INTRODUCTION

Hypercholesterolemia is a well-established risk factor for atherosclerotic cardiovascular disease (ASCVD) and cardiovascular risk reduction is proportional to low-density

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lipoprotein cholesterol (LDL-C) lowering[1,2]. European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) and American College of Cardiology/American Heart Society (ACC/AHA) guidelines impose statin therapy as first line treatment for reducing LDL-C levels and associated cardiovascular risk[1,2]. Ezetimibe addition to maximum tolerated statin is suggested for further LDL-C lowering[1,2]. However, a large proportion of patients do not achieve LDL-C goals under maximally tolerated lipid-lowering therapy or are statin intolerant[3]. This is also the case in Greece[4,5].

Monoclonal antibodies inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9) have been shown to effectively lower LDL-C levels and associated cardiovascular risk[6,7]. Two fully human PCSK9 inhibitors (PCSK9i) are available, alirocumab and evolocumab, administered by subcutaneous injection at 75/150 mg every two weeks and 140 mg every 2 weeks/420 mg once a month, respectively. In clinical studies PCSK9i lower LDL-C levels by 50-60% on top of maximally tolerated hypolipidemic treatment[8-14]. In addition, 3 randomized trials, FOURIER, ODYSSEY OUTCOMES and GLACOV, demonstrated that PCSK9i are associated with significant reductions of major cardiovascular events and atherosclerosis progression with an excellent safety profile[6,7,15]. Long-term studies have confirmed sustainability of LDL-C lowering up to 4 years[16-18].

In Greece PCSK9i are available since 2016 and are reimbursed in patients with either established ASCVD or familiar hypercholesterolemia (FH) and LDL-C level >100 mg/dL despite maximum tolerated high-intensity statin plus ezetimibe[19]. However, data on the use of PCSK9i in real-life in Greece is limited. We report herein clinical experience with PCSK9i from an outpatient University hospital lipid clinic over 2 year follow-up.

PATIENTS AND METHODS

Study population

In the present study, we included consecutive patients attending the lipid clinic at the University Hospital of Ioannina, Ioannina, Greece from 2016 to 2018 who were prescribed a PCSK9i. Reimbursement of PCSK9i treatment was granted to patients with either established ASCVD or FH and LDL-C level ≥100 mg/dL while on maximum tolerated lipid-lowering therapy (rosuvastatin target dose 20-40 mg or atorvastatin target dose 40-80 mg plus ezetimibe) and healthy lifestyle.

All patients prescribed PCSK9i were provided proper subcutaneous injection training. Patient characteristics, family history and concomitant medications were reported, and clinical examination and laboratory tests were performed at baseline visit, as well as after 2 months, 1 year and 2 years following PCSK9i administration. In addition, adverse events and compliance to PCSK9i therapy was reported during follow-up.

Data analysis

Analyses were performed descriptively via the Statistical Package for Social Sciences (SPSS) 21.0 software (SPSS, IBM corp). Continuous numeric variables are expressed as mean ± standard deviation and median (interquartile: IQR) if Gaussian or non-Gaussian distributed, respectively. Categorical data are presented as total number and percentage. An ANOVA with repeated measures was used to compare group means where the participants are the same in each group. Chi square test was used to compare categorical data among the alirocumab and evolocumab treated group. Two-tailed significance was defined as $p<0.05$.

Ethics

All participants gave written informed consent and the study protocol was approved by our institutional ethics committee. The research was performed according to the principles of the Declaration of Helsinki (1975).

RESULTS

Baseline patient characteristics (Table 1)

We included 37 patients [56.8% men, age 54 years (IQR: 50-71)]. Of those, 28 (76%) had established CVD [22 (60%) coronary artery disease and 6 (16%) a history of cerebrovascular event], 24 (65%) had HeFH and 3 (8%) had lower extremities arterial disease (LEAD)].

Nineteen individuals initiated evolocumab 140 mg (Q2W) and 18 received alirocumab [8 alirocumab 75 mg (Q2W) and 10 alirocumab 150 mg (Q2W)]. Of the alirocumab treated group, 6 patients maintained the dose of 75 mg (Q2W), while 2 patients were uptitrated to 150 mg (Q2W) after the 2-month follow-up. No significant difference in baseline characteristics was noticed between the 2 groups. Eight patients (5 patients intolerant to statins, 1 with homozygous FH and 2 with heterozygous FH) qualified PCSK9i treatment for primary prevention, while 29 patients for secondary prevention. Prior to initiation of PCSK9i, the vast majority of patients (90%) were on dual maximally tolerated LLT (79% on rosuvastatin 20-40 mg and 11% on atorvastatin 40-80 mg plus ezetimibe), 1 patient was on pitavastatin plus ezetimibe, 1 on pitavastatin monotherapy, 1 on ezetimibe monotherapy and 1 on colesevelam monotherapy (totally intolerable). No significant difference was observed in baseline characteristics among evolocumab and alirocumab treated groups (p=NS).

TABLE 1. Baseline patient characteristics

	All patients	Evolocumab	Alirocumab
Number	37	19	18
Age, years	54 (50-71)	52 (49-65)	55 (50-76)
	n (%)	n (%)	n (%)
Female	16 (43)	10 (53)	6 (33)
Current smoking	6 (16)	3 (18)	3 (15)
Coronary artery disease	22 (60)	9 (47)	13 (72)
Cerebrovascular disease	6 (16)	2 (11)	4 (22)
Hypertension	17 (46)	7 (37)	10 (56)
Diabetes	10 (27)	4 (21)	6 (33)
Carotid artery disease	9 (24)	6 (32)	3 (17)
Chronic kidney disease	4 (11)	1 (5)	3 (17)
FH			
HoFH	3 (8)	2 (11)	1 (6)
HeFH	24 (65)	8 (42)	16 (89)
LEAD	3 (8)	1 (9)	2 (11)
No statin	2 (5)	2 (11)	0
Rosuvastatin	29 (78)	15 (79)	14 (78)
Atorvastatin	4 (11)	1 (5)	3 (16)
Pitavastatin	2 (5)	1 (5)	1 (5)
Ezetimibe	35 (95)	17 (90)	18 (100)
Fenofibrate	3 (8)	2 (11)	1 (6)
Omega 3 fatty acids	1 (3)	0	1 (6)
Colesevelam	6 (16)	5 (26)	1 (6)
Intolerance to statins			
Partial intolerance	5 (14)	3 (16)	2 (1)
Total intolerance	3 (8)	3 (16)	0

Abbreviations: FH: familial hypercholesterolemia, LEAD: lower extremities arterial disease

Lipid profile (Table 2 and Figure)

PCSK9i administration yielded an additional 60% mean reduction in LDL-C and 42% mean reduction in TCHOL after 2 months on treatment ($p<0.05$). This reduction rate remained sustainable after 1 and 2 years on PCSK9i therapy. The LDL-C and TCHOL lowering rate was similar among evolocumab and alirocumab treated group after 2 months, 1 and 2 years (p=NS for between groups comparison). HDL-C was increased by 3% and triglycerides were decreased by 10% after 2-month PCKS9i treatment (p=NS). The overall percentage of patients attaining LDL-C target according to ESC/EAS 2016 guidelines[28] was 81% after 2-month PCSK9i therapy. Excluding homozygous FH patients (n=3), LDL-C was reduced by 63%, TGs by 12%, TCHOL by 42% and HDL-C was increased by 7% after 2 months on PCSK9i treatment. The 3 individuals with homozygous FH experienced a mean LDL-C reduction of 39% over a 2-year follow-up.

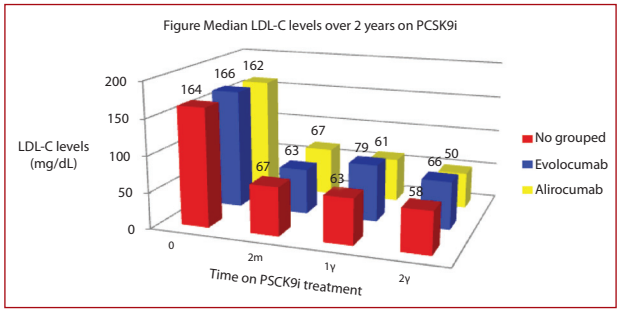

FIGURE 1. Median value of low-density lipoprotein cholesterol level (LDL-C) in all participants, according to treatment assignment and time on proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i).

Safety (Table 3)

The majority of patients (89%) did not report any adverse event during follow-up. One patient complained about backache (evolocumab group), one patient reported diarrhea and abdominal pain (evolocumab group), one patient a non-troublesome reaction at the injection site (alirocumab group) and one patient reported a 'pruritic rash' in the upper body which resolved after few days and was not seen with next doses of PCK9i (evolocumab group). The reported adverse events were not different between 2 treated groups. No patient dropped out of treatment. No CVD event was reported during follow-up.

DISCUSSION

The present study is one of the few investigating the efficacy and safety of PCSK9i administration in a clinical real life setting[20-26]. Randomized controlled clinical trials frequently enlarge the magnitude of LDL-C lowering rate due to rigorous patient monitoring and intensive lifestyle modifications[8-14]. Our study indicates a mean LDL-C reduction rate comparable with that of FOURIER and ODYSSEY clinical trials (approximately 60%) and similar with that achieved in real-life studies (50-63%)[20-26]. It also confirms that PSCK9i-related LDL-C reduction was sustained after 1 and 2 years on treatment with both evolocumab and alirocumab having comparable efficacy.

Three individuals (8.1%) with homozygous FH were responsive to PCSK9i on top of dual or triple hypolipidemic therapy and gained a mean percentage LDL-C level reduction of 39% over a 2-year follow-up. This is line with the

TABLE 2. Baseline and post treatment lipid panel of study participants (follow-up: 2 years)

	Baseline	2 months	Change from baseline	1 year	Change from baseline	2 years	Change from baseline
TCHOL, mg/dL							
All patients	240 (200-277)	140 (120-177)	-42%*	133 (113-169)	-45%*	116 (106-138)	-52%*
Evolocumab	241 (199-312)	142 (124-193)	-41%*	152 (127-195)	-37%*	144 (138-149)	-40%*
Alirocumab	239 (202-268)	138 (115-169)	-42%*	133 (112-140)	-44%*	113 (104-121)	-53%*
LDL-C, mg/dL							
All patients	164 (137-196)	67 (50-104)	-59%*	63 (51-96)	-62%*	58 (39-61)	-64%*
Evolocumab	166 (134-221)	63 (50-127)	-62%*	79 (52-106)	-52%*	66 (61-71)	-60%*
Alirocumab	162 (139-189)	67 (49-96)	-59%*	61 (50-72)	-62%*	50 (39-60)	-69%*
HDL-C, mg/dL							
All patients	51 (44-63)	53 (45-65)	3%	53 (45-63)	3%	53 (46-63)	3%
Evolocumab	51 (44-64)	53 (48-57)	3%	53 (48-60)	3%	53 (48-61)	3%
Alirocumab	49 (41-61)	50 (43-66)	2%	50 (43-60)	2%	50 (42-60)	2%
TGs, mg/dL							
All patients	116 (75-173)	104 (77-142)	-10%	104 (93-138)	-10%	104 (93-142)	-10%
Evolocumab	126 (89-173)	113 (82-144)	-10%	113 (100-147)	-10%	113 (98-147)	-10%
Alirocumab	103 (71-178)	93 (72-121)	-10%	93 (84-130)	-10%	93 (69-116)	-10%

Values are expressed as median (interquartile range: IQR), *p<0.05 for comparison values between baseline and during time. To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol and by 0.01129 for triglycerides.
Abbreviations: TCHOL: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TGs: triglycerides

mean reduction rate of LDL-C reported by one published real-life study (38%)[26]. In another trial in patients with homozygous FH, LDL-C was reduced by 20-65% after 12 weeks on PCSK9i. The magnitude of reduction was dependent on the underlying genetic defect with the greatest reduction noted in patients with PCSK9 gain of function mutations[14].

Of note, 90% of our patients were treated with high-intensity statins. Two previously published real-life cohorts reported treatment rates with high-intensity statin regiments in 49% and 66% of participants, respectively[23,26]. This discrepancy could be attributed to different PSCK9i approval criteria applicable in each country. In Greece, LDL-C levels above treatment target despite high-intensity statin plus ezetimibe administration or maximally tolerated LLT comprises a precondition for PCSK9i reimbursement[19]. Of interest, in our study the percentage of LDL-C goal attainment was 81%. This proportion is higher than other cohorts reporting LDL-C target achievement by 55-76%[20,22,24,26,29].

Safety

Our data verify the favorable safety profile of both evolocumab and alirocumab in daily clinical practice in line with randomized clinical trials. Minor adverse events were manifested by 6% of patients, a lower incidence than that reported in randomized clinical trials; there were no differences between evolocumab and alirocumab treatment groups. These side effects did not lead to treatment discontinuation and resolved spontaneously. Notably, in our study no treatment discontinuation was observed in contrast with other cohorts reporting a discontinuation range of 2.5-15.0%, mainly due to non-adherence[20,22,24,26]. Interestingly, 8.1% of patients being intolerant to statins due to muscle symptoms did not report any muscle event with PCSK9i administration. In GAUSS-3 there was a higher percentage of muscle symptoms in ezetimibe compared with evolocumab group[27].

Limitations

This study comprises real-life data from a relatively small number of patients attending a university outpatient lipid clinic. In this view, our findings may not be generalizable to other populations particularly to hospitals those without lipid clinics or to the private practice.

In conclusion, PCSK9i administration in a real-life clinical setting was associated with potent LDL-C reductions and a favorable safety profile during a 2-year follow-up

TABLE 3. Baseline and post treatment laboratory reports of study participants (follow-up: 2 years)

Laboratoryreports	Baseline	2 months	Change from baseline	1 year	Change from baseline
AST, IU/L					
All patients	25 ± 7	29 ± 18	16%	26 ± 7	4%
Evolocumab	24 ± 7	33 ± 24	38%	25 ± 8	4%
Alirocumab	26 ± 7	24 ± 8	-8%	27 ± 6	4%
ALT, IU/L					
All patients	29 ± 11	33 ± 25	14%	31 ± 12	7%
Evolocumab	30 ± 12	37 ± 33	23%	34 ± 15	13%
Alirocumab	28 ± 10	28 ± 12	0%	29 ± 11	4%
CK, IU/L					
All patients	129 (85-151)	123 (88-164)	-5%	180 (123-331)	40%
Evolocumab	137 (112-145)	129 (93-191)	-6%	159 (134-406)	16%
Alirocumab	98 (60-155)	100 (63-155)	2.%	180 (122-322)	82%
Glucose, mg/dL					
All patients	98 (95-106)	100 (95-111)	2%	97 (93-117)	-1%
Evolocumab	97 (94-101)	99 (95-106)	2%	97 (90-101)	0%
Alirocumab	100 (96-111)	109 (90-124)	9%	106 (93-118)	6%
Creatinine, mg/dL					
All patients	0.94 ± 0.23	0.97 ± 0.23	3%	0.94 ± 0.30	0%
Evolocumab	0.87 ± 0.12	0.93 ± 0.12	7%	0.85 ± 0.12	-2%
Alirocumab	1.02 ± 0.29	1.02 ± 0.30	0%	0.98 ± 0.35	-4%
eGFR, mL/min/1.73 m^2					
All patients	83.3 ± 18.93	81.24 ± 16.19	-2%	84.21 ± 22.87	1%
Evolocumab	88.31 ± 14.93	84.23 ±12.37	-5%	88.75 ± 13.40	0%
Alirocumab	78.31 ± 21.56	78 ± 19.53	-0%	82.40 ± 26.13	5%

Values are expressed as median (interquartile range: IQR) and as means ± SD.
Abbreviations: AST: aspartate transaminase, ALT: alanine transaminase, CK: creatine kinase, eGFR: estimated glomerular filtration rate

comparable to what is reported in randomized clinical trials.

Authorship

Dr. G. Anastasiou contributed to the conception and design, acquisition, analysis and interpretation of data and been involved in drafting the manuscript. Dr. E. Christopoulou and Dr. T. Dimitriou contributed to the analysis and interpretation of data. Dr. G. Liamis, Dr. H. Milionis and Prof. M. Elisaf have been involved in critically revising the manuscript. Dr. E. Liberopoulos has given the final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

AG, EC, and TD have nothing to declare; EL has participated in educational, research and advisory activities sponsored by Astra-Zeneca, MSD, Lilly, Bayer, Amgen, Sanofi, Boehringer-Ingelheim, Novartis, Novo Nordisk and Servier; HM reports receiving honoraria, consulting fees and non-financial support from healthcare companies including Amgen, Bayer, MSD, Mylan, Pfizer, Sanofi, and Servier; GL reports personal fees from Angelini, Bayer, Menarini and Sanofi; Professor M. Elisaf reports honoraria

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ΠΕΡΙΛΗΨΗ

PCSK9 αναστολείς: Η επαναστατική θεραπεία μείωσης των λιπιδίων στα πλαίσια της καθημερινής πρακτικής. Κλινική εμπειρία 2 ετών

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Παθολογική Κλινική Τμήματος Ιατρικής, Πανεπιστήμιο Ιωαννίνων

Σκοπός: Οι αναστολείς της πρωτεΐνης convertase subtilisin/kexin type 9 (PCSK9) έχουν αποδεδειγμένη ασφάλεια και αποτελεσματικότητα στη μείωση των χαμηλής πυκνότητας λιποπρωτεϊνών (LDL-χοληστερόλη) και του καρδιαγγειακού κινδύνου. Τα δεδομένα σχετικά με την κλινική εφαρμογή των PCSK9 αναστολέων στην Ελλάδα είναι περιορισμένα. Για το σκοπό αυτό, περιγράφουμε την εμπειρία 2 ετών από την εφαρμογή των PCSK9 αναστολέων σε ένα Ιατρείο Λιπιδίων Πανεπιστημιακού Γενικού Νοσοκομείου. **Ασθενείς και Μέθοδοι:** Πρόκειται για μια αναδρομική μελέτη ασθενών οι οποίοι έλαβαν για πρώτη φορά PCSK9 αναστολέα στο χρονικό διάστημα 2016-2018. Οι ασθενείς είχαν είτε εγκατεστημένη καρδιαγγειακή νόσο (ΚΑΝ) και/ή οικογενή υπερχοληστερολαιμία (FH) και επίπεδα LDL-χοληστερόλης >100 mg/dL παρά τη λήψη της μέγιστης ανεκτής δόσης υψηλής ισχύος στατίνης και εζετιμίμπης. Τα δημογραφικά στοιχεία των ασθενών, το ιατρικό ιστορικό, η συγχορηγούμενη φαρμακευτική αγωγή και τα εργαστηριακά αποτελέσματα καταγράφηκαν κατά τη διάρκεια των επισκέψεων. **Αποτελέσματα:** Στη μελέτη συμμετείχαν 37 ασθενείς (μέση ηλικία 52 ετών, 56.8% άνδρες). Από τους ασθενείς, 28 (76%) είχαν εγκατεστημένη ΚΑΝ και 27 (74%) FH. Σχετικά με τη φαρμακευτική αγωγή, 33 ασθενείς (89%) ελάμβαναν υψηλής ισχύος στατίνη, ενώ 35 ασθενείς (95%) ελάμβαναν επίσης και εζετιμίμπη 10 mg. Η προσθήκη των PCSK9 αναστολέων (51% εβολοκουμάμπη 140 mg κάθε 2 εβδομάδες, 22% αλιροκουμάμπη 75 mg κάθε 2 εβδομάδες και 27% αλιροκουμάμπη 150 mg κάθε 2 εβδομάδες) συσχετίστηκε με μείωση της ολικής χοληστερόλης κατά 42% και της LDL-χοληστερόλης κατά 59% μετά από 2 μήνες θεραπείας ($p<0.05$). Τα ανωτέρω ποσοστά των μειώσεων παρέμειναν σταθερά μετά από 1 και 2 χρόνια θεραπείας. Τριάντα ασθενείς (81%) επέτυχαν το θεραπευτικό στόχο για την LDL-χοληστερόλη με τη λήψη των PCSK9 αναστολέων. Τέσσερις ασθενείς (11%) εκδήλωσαν ανεπιθύμητες ενέργειες ελάσσονος σημασίας. Δεν αναφέρεται διακοπή της θεραπείας στη διάρκεια των 2 ετών. **Συμπέρασμα:** Στα πλαίσια της καθημερινής κλινικής πρακτικής, η προσθήκη των PCSK9 αναστολέων στη μέγιστη ανεκτή υπολιπιδαιμική αγωγή συσχετίστηκε με μείωση της LDL-χοληστερόλης του ίδιου μεγέθους με τις τυχαιοποιημένες κλινικές δοκιμές. Οι μειώσεις αυτές διατηρήθηκαν στη διάρκεια της 2ετούς παρακολούθησης.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *PCSK9 αναστολείς, δυσλιπιδαιμία, οικογενής υπερχοληστερολαιμία, στατίνες, καρδιαγγειακή νόσος, εζετιμίμπη*

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