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Original Research

Retrospective study on clinical efficacy of Evolocumab in high-risk ASCVD patients

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Abstract

Objective: This study evaluated the effectiveness of Evolocumab by measuring achievement target LDL-C among high-risk ASCVD patients in the UAE. **Method:** A retrospective observational study included 27 patients with high-risk ASCVD receiving Evolocumab 140 mg/mL SC injection every 2 weeks. The effectiveness of Evolocumab is measured by the mean reduction in LDL-C levels from baseline and achieving target LDL levels according to ECS/EAS guideline during average follow up period. **Results:** The average (SD) age of the patients is 52 (10) years. Majority of the patients were male (n=22), smokers (40.9%), overweight or obese (78%), had a history of hypertension (59.3%), MI (55.5%) and diabetes (40.7%). The patients were on Evolucomab therapy due to persistently elevated LDL-C (n=25) or statin intolerance (n=2). During the average follow up period of 42 weeks,14 patients (51%) achieved target LDL-C level. During this period, LDL-C and TC levels reduced from 3.51(1.3) mmol/L to 1.9 (1.2) mmol/L and from 4.97 (1.4) mmol/L to 1.62 (1.09) mmol/L, respectively post Evolocumab therapy. **Conclusion:** The reduction was statistically significant. However, the reduction of TG levels and the increase in HDL level was not significant. Evolocumab reduces LDL-C and TC levels significantly in high-risk ASCVD patients in a tertiary hospital in the UAE population.

Keywords: evolocumab, saftey, effectiveness, United Arab Emirates

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) includes acute myocardial infarction, stable and unstable angina, stroke, transient ischemic attack (TIA), coronary artery revascularization, and peripheral artery disease (PAD) of atherosclerotic origin. High-risk ASCVD patients are those patients with a prior cardiovascular event or those with other uncontrolled cardiovascular disease (CVD) risk factors. High cholesterol levels in addition to other factors such as smoking, family history, high blood pressure, uncontrolled blood sugars, obesity, and sedentary lifestyle increase the risk of ASCVD.[1]

Globally the prevalence of CVD risk factors continues to rise, currently cardiovascular diseases (CVD) are one of the leading causes of mortality.[2] A similar trend of a high prevalence of cardiovascular diseases and ASCVD, in particular, is a key challenge in UAE health care. According to the reports from the Ministry of Health and Prevention, CVD is a leading cause of death in the UAE.[3] Evidence shows that in UAE population have high CVD risk. Furthermore, results of high-risk CVD complications due to major factors in female due to high TC and low HDL level, in male the history of smoking and age play a role in increasing the incidents of CVD in UAE.[4]

According to American Heart Association, lipid-lowering therapy plays a key role in reducing the risks associated with ASCVD. Various statin (moderate, high intensity statins) and non-statin lipid-lowering therapy (ezetimebe, PCSK9 inhibitors) are available to lower high LDL-C levels. Statins, for instance, decrease the risk of ASCVD by up to 50%. However, non-adherence to statin therapy and statin intolerance are common drawbacks. In addition, even with the optimal use of statin therapy, there is residual risk of ASCVD.[5]

Evolucmab is an injectable medication with higher efficacy in treating dyslipidemia. It is recognized as a strong and effective agent to reduce LDL levels without producing serious side effects. Evolocumab is approved by the food and drug administration (FDA) in 2015 and the European medical agency (EMA) because it significantly reduces LDL-C levels and CVD events among patients with a high risk of ASCVD.[6] Subcutaneous injection of Evolocumab 140 mg every 2 weeks or 420 mg once monthly is approved by FDA for adults with established cardiovascular disease or primary hyperlipidemia (including HeFH). Though statins are known as standardized treatment PCSK9 inhibitor has played an important role in FH. It is a cost-effective regimen and perfect for patients who are already on maximally tolerated statin dose.[7]

Multiple studies have demonstrated the effectiveness of Evolocumab. When Evolocumab is used as an adjunct therapy with statins among patients with high LDL levels (LDL >100mg/dL) and among patients with recurrent CVD events, it reduced LDL levels by 70%.[8] Enhanced efficacy of Evolocumab is also observed among patients who experienced recent acute cardiovascular events. Another clinical trial suggests that

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Evolocumab is safe for use and reduces the risk of cardiovascular events by up to 70%.[9] Studies suggest that aggressive treatment with statin and PCSK9 inhibitors combined has a safer profile index than other LDL-C lowering agents.[9]

Evolocumab is known to be safe and effective according to the American heart association (AHA) and the European Society of Cardiology (ESC) guidelines. The only factors that limit the use of evolocumab include the need for subcutaneous injection and minor side effects such as influenza-like symptoms, upper respiratory tract infection, arthralgia, and injection-site reactions, the high cost, and lack of long-term safety data.[10]

To our knowledge, there is sparse data regarding the efficacy of Evolocumab in the UAE population. Therefore, there is a need to conduct a study to evaluate the efficacy of Evolocumab among high-risk ASCVD patients in the UAE. This study is set to evaluate the efficacy of Evolocumab to reduce LDL-C levels in patients with high-risk ASCVD. Patient-related factors and clinical factors associated with the efficacy of Evolocumab will also be explored. Also, the study can give insight regarding the prevalence of ASCVD risk factors and the incidence of ASCVD complications among patients treated with Evolocumab at Zayed Military Hospital during the follow-up period. The findings of this study can serve as preliminary data for future researchers and add to the real-world evidence of efficacy Evolocumab in a different population.

METHODS

Study design and participants

This retrospective observational, was undertaken in Zayed military hospital. Data was extracted from electronic medical records using standardized data collection form. Data collection started after ethical approval is obtained February 28, 2021 and was concluded on June 15, 2021.

All patients included in the study aged 18 years or older who are diagnosed with high-risk ASCVD receiving Evolocumab as an add on therapy to maximum tolerated dose of statin or ezetimibe. Patients without high-risk ASCVD or no follow-up data on LDL-C level after the start of lipid lowering therapy and pregnant women are excluded.

Evolocumab is an expensive and relatively new drug, there are very limited number of patients receiving this medication. All patients receiving the medication were screened for eligibility.

Study instrument & validation procedure

A standardized data collection form designed based on pivotal clinical trials of Evolocumab and similar lipid lowering therapies and based on current information on American Heart Association (AHA) and European society of cardiology (ECS) guidelines.[12]

The data collection form includes demographic data, ASCVD risk factors, laboratory data and relevant clinical outcomes (e.g any CVD related hospitalization or death). Relevant demographic data (age, gender, ethnicity, height, weight, BMI, smoking, physical activity), clinical data including laboratory results and ASCVD risk factors (total cholesterol, LDL-C, HDL-C, triglyceride, and liver and kidney function test, CK levels, CRP, family history of ASCVD, compliance to medication, comorbidities and concurrent medications and history of ASCVD events) extracted from medical records for each patient.

The efficacy of the drug measured based on the reduction in LDL-C levels from baseline and by the achievement of target LDL-C levels for patients during follow-up. The target LDL-C to be achieved by individual patients was determined by SCORE CVD risk estimation according to ECS guideline.[12] Estimation of incidence rates of composite outcome of death and hospitalization due to cardiovascular events during follow up period.

Statistical analysis

Summary of categorical patient characteristics and the proportion of patients who achieve target LDL levels presented using percentages and frequency. By using chi-square test, the association between patient related factors and achievement of LDL target is examined. For sparse data fisher exact test was used. All data analysis conducted using SPSS Statistics version 26. P value of < 0.05 considered statistically significant for all tests.

RESULTS

The baseline characteristics of study population is presented in Table 1. The average (SD) age of the patients is 52 (10) years. Table 1. Describe the demographic data, patients spirited into 4 Age groups majority between age of 41-50 and 61-70 (29.6%). Most of patients included in this study are male 22% female are less 18.5%. Population nationality most of them are UAE citizen and BMI represented mostly with obese patients 55.5%. Most of the patients are Non-smokers 48% and a few are X-smoker 11.1%. Majority of patients are having family history of dyslipidemia 74% and 55.5% of them having a family history of ASCVD.

Table 2 shows the underlying diseases and patients medication history, the current diagnosis and comorbidities of patients. Most of patients 59.3% are having hypertension and history of MI 55.5%. Most of the patients are with history of revascularization and undergo PCI procedure 55.5% and 25.9% did CABG revascularization procedure. Baseline medication shows that 85% of patients before starting Evolocumab were on combination of high intensity Statin and Ezetimibe, few of patients 7.4% were having statin intolerance so they were on Ezetimibe alone and 7.4% patients in statin alone.

Figure 1 shows the main reason of initiating Evolocumab ether due to Persistently elevated LDL-C (25 patients) despite maximally tolerated high statin therapy and ezetimibe and (2 patients) has an indication of Intolerance to statins**.** Majority of patients in this study started Evolocumab due to persist elevated LDL level above. All of the patients were receiving the standard dose of Evolocumab 140 mg injected every 2 weeks.

Table 3 shows Evolocumab duration of treatment, the average

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Table 1. Baseline characteristics

Patient characteristics	Number of patients (n)	Percentages (%)
Age group (years)		
30-40	4	14.8%
41-50	8	29.6%
51-60	7	25.9%
61-70	8	29.6%
Gender		
Male	22	81.4%
Female	5	18.5%
Nationality		
UAE	24	88.8%
Non-UAE	3	11.1%
BMI		
Obese (>30kg/m2)	15	55.5%
Overweight (25-29Kg)	6	22.2%
Normal (18.5 - 24.9Kg)	6	22.2%
Smoking history		
Smoker	11	40.7%
Ex-smoker	3	11.1%
Non-smoker	13	48.1%
Family history		
History of ASCVD	15	55.5%
History of Dyslipidemia	20	74%

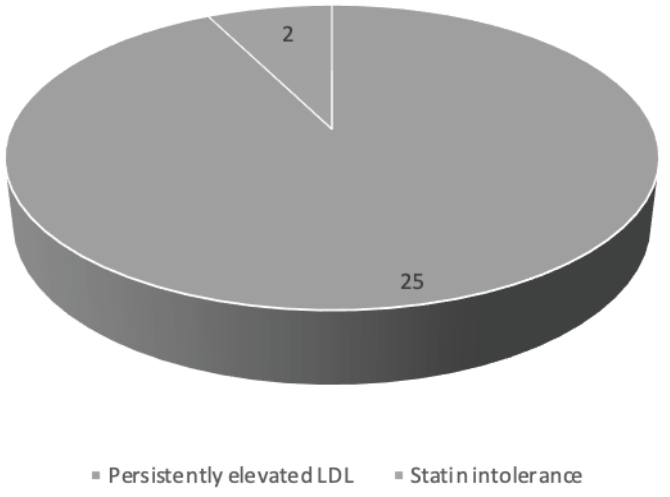

Figure 1. Indication of Evolucumab

Table 2. Underlying diseases and patient's medication history

Disease and medication history	Number of patients (n)	Percentages (%)
Current diagnosis		
CAD	5	18.5%
Unstable Angina	7	25.9%
STEMI	8	29.6%
NSTEMI	7	25.9%
Comorbidities		
Hypertension	16	59.3%
Diabetes mellitus	11	40.7%
peripheral arterial disease	3	11.1%
Hx stroke and TIA	1	3.7%
CHF	2	7.4%
Hhistory of MI	15	55.5%
History of Revalscularization		
Prior history of CABG	7	25.9%
Prior history of PCI	15	55.5%
Prior history of CABG and PCI	1	3.7%
No History of CABG or PCI	4	14.8%
Baseline medication		
Statin alone	2	7.4%
Statin+ ezetimibe	23	85%
Ezitimibe alone	2	7.4%

Table 3. Change in lipid profile post Evolocumab therapy

Lipid profile	Results
Baseline TC	4.97 mmol/L (1.4)
Post Evolocumab	3.36 mmol/L (1.38)
Change in TC	2.04 mmol/L (1.25)
Statistics p-value (Wilcoxon test)	0.001*
Baseline TG	2.2 mmol/L (1.4)
Post Evolocumab	1.62 mmol/L (1.09)
Change in TG	0.495 mmol/L (1.26)
Statistics p-value (Wilcoxon test)	0.05
Baseline LDL	3.51 mmol/L (1.3)
Post Evolocumab	1.9 mmol/L (1.2)
Change in LDL	1.82 mmol/L (1.16)
Statistics p-value (Wilcoxon test)	0.001*
Baseline HDL	0.98 mmol/L (0.2)
Post Evolocumab	0.99 mmol/L (0.25)
Change in HDL	-0.028 mmol/L (0.16)
Statistics p-value (Wilcoxon test)	0.38
Average Duration of Treatment in	42 weeks

follows up period is 42 weeks with minimum follow up period of 9 weeks up to maximum follow up period of 91 weeks. The lipid profile shows the average change pre and post Evolocumab treatment. Results shows significant reduction p-value (0.001) from the base line in TC (total cholesterol) 4.97 (1.4) to post Evolocumab 1.62 (1.09) and the change in TC from base line was 2.04(1.25). TG (triglyceride) level of reduction was insignificant p-value (0.05) from base line 2.2 (1.4) to post Evolocumab 1.62 (1.09) and the change was 0.495 (1.26). LDL shows a significant reduction p-value (0.001) from base line

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3.51(1.3) to post Evolocumab 1.9 (1.2) and the change from baseline 1.82 (1.16). HDL level shows an increase in value but not significant p-value (0.38) the baseline was 0.98 (0.2) and post Evolocumab treatment was 0.99 (0.25) with a change from baseline -0.028 (0.16).

Table 4 shows the association of demographic and clinical factors on achieving the target LDL level during the follow up period of 42 weeks. Gender, nationality and smoking history does not have significant association with achieving the target LDL level. BMI does not have a significant impact on achieving target LDL level. Other factors like history of MI, ASCVD, dyslipidemia and history of revascularizations also has no impact on achieving target LDL levels.

DISCUSSION

This retrospective observational study assessed the effectiveness of evolocumab therapy in reducing LDL-C level in clinical practice among 27 patients with ASCVD treated in Zyed Military Hospital in the United Arab Emirates.

Due to high cost, the need for preauthorization and approval, only few patients were receiving this medication at this center. Before receiving Evolocumab these patients were on high intensity statin therapy or combination of statin and ezetimibe therapy. Evolocumab was added due to persistently high LDL-C levels despite lipid lowering therapy or due to statin intolerance. All the patients received the medication in accordance with recommendations of ESC/EAS guideline showing that the research setting encourages an evidence-based practice.[1]

Relatively younger adults are at risk of CVD events in the gulf countries compared to other regions of the world. This can be depicted from the average (standard deviation) age of study population which is 52 (10) years. The majority of the study participants are UAE citizens, male and overweight. Higher number of male patients is anticipated due to the setting of the study, which is a military hospital. In addition, higher prevalence of ASCVD is common among male patients than female patients due to protective effect of estrogen in women aged less than 55 years.[11] High BMI has a detrimental impact on the cholesterol level and lipid profile and it is associated with increased the risk of developing comorbidities like cardiovascular disease, hypertension and diabetes.[12] A significant proportion of study subjects are current smokers (40.9%) and has a family history of ASCVD and dyslipidemia.

Table 4. Association between demographic and clinical factors with achievement of target LDL-C level

Factors		**Achieved**	**Not Achieved**	**P-value**
Gender	Male	11	11	0.999
	Female	3	2	
UAE		11	13	0.22
Non-UAE		3	0	
Smoking History	Smoker	7	4	0.13
	Non-smoker & X-smoker	7	9	
BMI	Obese & Overweight	7	14	0.06
	Normal	5	1	
Age Group (years)	30-40 & 41-50	5	7	0.999
	51-60 & 61-70	7	8	
Family history of ASCVD		7	8	0.704
No history of ASCVD		7	5	
Family history of Dyslipidemia		10	10	0.999
No Family history of Dyslipidemia		4	3	
Hypertension		8	5	0.999
No Hypertension		6	8	
Diabetes mellitus		6	5	0.999
No Diabetes mellitus		8	8	
History of previous MI		8	7	0.999
No History of previous MI		6	6	
Coronary Artery Disease	Unspecified type CAD &Unstable Angina	6	6	0.417
	STEMI	3	5	
	NSTEMI	5	2	
History of revascularization	CABG	4	4	0.17
	PCI	7	9	

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There is high prevalence of CVD risk factors among the study participants. The top three comorbidities are hypertension, myocardial infraction and diabetes mellitus. All except four patients had undergone PCI, CABG or both procedures.

Cardiovascular risk reduction through risk factor control is considered a major public health priority in the UAE. Life style modifications (dietary modification, smoking cessation, and lowering of body weight, exercising) as well as medications to lower blood pressure, lipid or glucose levels are crucial. The PREDIMED trial has shown that Mediterranean diet can result in body weight reduction and cut the risk of CV events by 30%. Other studies have also shown dietary modification and physical activity can have a favorable impact on HDL-C level and TG levels.[12,13] High proportion of smokers in this study calls for action to improve smoking status considering the high risk of ASCVD in these patients. Due to government led programs to curb the smoking rates in the UAE currently, the prevalence of smoking in UAE is less compared to other countries in the Middle East.[14]

Studies show that lipid lowering plays and important role in the control of ASCVD risk. The patients in this study would benefit from significant lipid lowering therapy to reduce their risk of ASCVD. The target LDL-C levels for each patient is determined using the baseline data at Evolocumab initiation using scores of systematic coronary risk evaluation (SCORE) of the ESC/EAS guideline. The patients were categorized as high-risk patients or very high risk ASCVD according to this risk stratification tool. The target LDL-C level for high-risk patients is 1.8 mmol/L while those with very high risk is 1.4 mmol/L.[1,15] According to this targets 51 percent of the patients in this study achieved target LDL-C levels during average follow-up duration of 42 weeks post Evolocumab therapy. The average duration of follow-up among patients who achieved LDL-C levels and those who did not achieve did not differ significantly despite the fact that duration of follow-up can influence the level of LDL-C reduction as reported in OSLER-1, OSLER-2 and DESCARTES trial.[16,17]

There was also a significant reduction in the average LDL-C and TC levels from baseline. However, the reduction in TG and the increase in HDL-C levels post Evolocumab therapy was not significant. ESC guideline highlighted a meta-analysis of observational studies that linked high TC reading with increased mortality and cardiovascular risk.[12] The baseline average TC for the study participants was 4.97 (1.4) mmol/L before starting Evolocumab. The FOURIER trial showed similar results of reduction in LDL-C from baseline 2.4 to 0.78 in a duration of 42 weeks but this trial shows an adverse event of injection site reaction that was not found in this study.[18] Evidence from MENDEL-2 trial shows increasing HDL when Evolocumab was given as monotherapy by 6%-9% and in ODYESSY MONO trial HDL increase by 6%.[16]

None of the demographic and clinical characteristics were associated with achievement of target LDL-C levels in this study. Prior studies show that age and gender can have impact on levels of cholesterol. Independent predictor factors for attainment of 2019 ESC/EAS LDL-C goals were to be male, smoking and the use of statins with ezetimibe.[19] In women above 65 years of age, the level of HDL is reduced resulting in increased risk of coronary artery diseases.[20] In addition, increased age is an established factor for developing CVD mortality and morbidity.[21] The lack of association may be linked to limited power of the study due to small sample size. Pooled analysis study shows age has significant influence in achieving target LDL-C reduction which is more in younger population. Also, gender has significant impact, male shows grater LDL-C reduction than female.[22]

The use of Evolocumab with high intensity Statin and Ezetimibee, have beneficial results in reducing the Coronary artery disease events which require interventions such as CABG and PCI revascularization procedure by 22%.[11] Considering high number of patients in this study with prior revascularization history, the use of Evolocumab in the long-run may help reduce the need for this intervention for recurrent events.

During the follow-up period there was no documented CV events (such as MI, Stroke, revascularization) and hospitalization for CV events in our setting. The positive impact of Evolocumab on reducing CV events and costs due hospitalization has been reported.[23,24]

Limitation

This study has several limitations: Firstly, the small sample size and relatively short follow-up period limit the power of the study and the conclusion. High cost, the need for consultant prior authorization, and the long time taken for approval of Evolucumab therapy was the main reason for few numbers of patients on the drug. Secondly, the result of this study cannot be generalized to the whole UAE population. Thirdly, the lipid profile for each patient was measured at different times and this did not allow to evaluate the reduction of LDL-C levels at same time for all patients.

CONCLUSION

This study give insight on real world evidence of effectiveness and safety of Evolocumab among patients with ASCVD treated at Zyed military hospital in the UAE. Over an average period of 42 weeks, Evolocumab significantly reduced in LDL-C and TC levels in patients with ASCVD. During this period only, half of the study population achieved target LDL-C. The patients included in this study would benefit from risk factor modifications to reduce the risk of recurrent CV events. Weight reduction and smoking cessation programs are needed. There was no documented adverse CV events and discontinuation of drug therapy during the follow-up period. Studies with bigger sample size and longer duration of follow up are needed to reliably assess the effectiveness of Evolocumab in the UAE population. This study can be considered as a preliminary data.

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