J Cardiovasc Disease Res., 2018; 9(2):45-53
A Multifaceted Peer Reviewed Journal in the field of Cardiology
www.jcdronline.org | www.journalonweb.com/jcdr

Review Article

Evolocumab in Combination with Statins for CVD Risk Reduction: An Evidential Review

Roopa Satyanarayan Basutkar[1], Tenzin Tsundue[1], Hema Siva[1], Raja Durai[1], Sivasankaran Ponnusankar[1,2]*

[1]*Department of Pharmacy Practice, JSS College of Pharmacy, Ooty, The Nilgiris, Tamilnadu, INDIA.*
[2]*JSS Academy of Higher Education and Research, Mysuru, Karnataka, INDIA.*

ABSTRACT

Objectives: The objectives of this evidential review is to conceptualize the ability of Evolocumab in combination with statins for reducing low density lipoprotein concentrations (LDL-C) and its impact on other lipid parameters, ultimately leading to cardiovascular disease risk reduction. **Background:** For years, atherosclerotic cardiovascular diseases have been one of the leading burdens on healthcare system attributed to high rate of mortalities. The primary treatment approach included the use of statins as the first line of drug. However, despite its side effects, high amount of residual cholesterol that would be left behind and contributes as a risk factor for future cardiovascular events. **Methods:** The search included PubMed, BioMed Central (BMC), Clinical key, Scopus, ScienceDirect and the Cochrane CENTRAL, using the following search terms and key words: 'PCSK9 inhibitors', 'PCSK9', 'AMG 145' or 'Evolocumab' in association with 'CVD risk reduction' and 'statins'. The search was restricted to trials conducted after 2012. **Results and Discussion:** Evolocumab showed greater degree of LDL-C reduction as compared with placebo and only statins group, irrespective of statin dose. A pooled estimate of 58.5% reduction in LDL-C reduction is caused by Evolocumab and thereby playing a major role in both treatment and the prevention of further cardiovascular events. Furthermore, Evolocumab when used in combination with statins showed a much higher reduction in LDL-C levels and thereby resulting in an optimised lipid management. **Conclusion:** It is well evident that Evolocumab in combination with statins is very efficacious in LDL-C reduction and hence atherosclerotic cardiovascular risk reduction. Yet, further studies are required to define the dose of statins to be incorporated in the combination.

Key words: LDL-Concentration, LDL-receptor, PCSK9 inhibition, Hypercholesterolemia, Evolocumab, Atherosclerotic cardiovascular disease.

Correspondence
Dr. Sivasankaran Ponnusankar
Professor and Head,
[1]Department of Pharmacy Practice, JSS College of Pharmacy, Udhagamandalam – 643 001, The Nilgiris. Tamilnadu, INDIA.
[2]JSS academy of higher education and research, Mysuru, Karnataka, INDIA.
Ph.no: 423-2443393
E-mail address: ponnusankar-sivas@gmail.com

Submission Date: 23-05-2018;
Revision Date: 12-06-2018;
Accepted Date: 03-07-2018.
DOI : 10.5530/jcdr.2018.2.13

INTRODUCTION

Currently available clinical guidelines recommend statin therapy as the first line drug for the treatment of dyslipidaemia. In patients with statin intolerance particularly due to myalgia and other adverse effects, hypercholesterolemia is treated with other lipid lowering therapies (bile acid sequestrate or nicotinic acid or cholesterol absorption inhibitors) with a backbone therapy of statin, usually at low doses or maximal tolerated doses.[1-2]

Familial hypercholesterolemia (FH) is caused by genetic abnormality which mainly contributes to the risk of coronary heart diseases.[3] Furthermore it is classified into heterozygous and homozygous hypercholesterolemia and subsequently subjects generally develop these before the age of 55 to 60 and 20 years respectively. Appropriate and early diagnosis and treatment of this not only reduces the risk of cardiovascular events but also the rate of mortality.[4-5]

Lifestyle modifications followed by statin therapy are the primary approach to any atherosclerotic events. Even though statins cause significant reduction in Low Density Lipoprotein Concentration (LDL-C), there is a risk of residual cholesterol left behind in the blood stream.[6] To address this residual cholesterol, a new group of drugs called Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK-9) inhibitors are showing unparalleled benefit. PCSK9 initiates the degradation of the Low Density Lipoprotein Receptor (LDL-R) and has played a vital role in lipid lowering efficacy, since it was discovered in 2003. In the body, PCSK9 is self-cleaved, secreted, and tightly bound to the epithelial growth factor-A (GF-A) like domain of the LDL-R. Heterozygous mutation in apolipoprotein B (ApoB) leads to ApoB's LDLR binding domain and loss of functional mutations in LDL-R.

LDL-R, or heterozygous gain of functional mutations in PCSK9 are well known genetic causes of heterozygous familial hypercholesterolemia (HeFH).[7] Consecutively homozygous familial hypercholesterolemia (HoFH), is a result of homozygous, or often, from compound heterozygous mutations in either the LDL-R or Autosomal Recessive Hypercholesterolemia (ARH) genes. This in turn renders the LDL-R recycling leading to the down regulation of LDL-R activity.[8] Consequent loss of LDL-R leads to elevated concentration of LDL in the blood, the primary regulator of atherosclerosis.[9] Evolocumab is a human monoclonal antibody to PCSK9, thereby causing significant reduction in the blood LDL-C.

Evolocumab has been approved by the Food and Drug Administration (FDA), USA and the European Medicines Agency (EMEA) for the treatment of hypercholesterolemia and in combination therapy with the maximal tolerated doses of statins and other lipid lowering therapies. It has shown benefit in additional therapeutic approaches like HeFH, HoFH and atherosclerotic cardiovascular disease (ASCVD).[10] The currently available doses of Evolocumab are 140mg/mL in a single-use prefilled syringe (every 2 weeks-Q2W) and 420mg/3.5mL in a single-use system (QM Subcutaneous injection).[11]

The primary objective of this review is to emphasize the ability of Evolocumab in combination with statins, in reducing LDL-C and other lipid parameters for CVD risk reduction. The secondary objective briefs on the safety aspects of Evolocumab.

METHODOLOGY

Literature search

Our approach for selection of studies for the review was to identify all the randomized controlled trials (RCTs) that were conducted from Phase II of clinical trials and beyond. The need to include Phase II and Phase III studies for our review is emphasized on the dosage, safety and over all

efficacy of Evolocumab in CVD patients. As the outcomes in Phase III trials are to determine the efficacy of a drug while Phase II of a clinical trial is conducted to determine the optimal dosing information.

The databases that were searched included PubMed, BMC, Clinical Key, Scopus, ScienceDirect and the Cochrane CENTRAL, using the following search terms and key words: 'PCSK9 inhibitors', 'PCSK9', 'AMG 145', 'Evolocumab', 'CVD risk reduction' and 'statins'. The references of the final listings were manually checked, but however, we applied search restrictions to abstracts only and non-English papers. The scheme of selection of papers are represented in Figure 1.

Study selection

From the pool of articles, the eligibility screening was performed by two independent authors (TT and HS). The inclusion and the exclusion criteria are described in the Table 1. No restrictions were placed on any of the study populations or sample size. Studies including animals, which were not randomized and other studies not pertaining to our objectives were excluded.

Outcome

The primary outcome was the percent reduction in LDL-C from baseline. Secondary outcomes included changes in other lipid profiles. Safety outcomes included the rate of common adverse events, treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs) and the frequency of injection site reactions.

Data collection

Two independent reviewers (TT and HS) abstracted the data using a standardized data extraction form. And in case of disagreements, a third reviewer (RD) checked the data for her opinions. The data extraction process included: trial title, author names, year of publication, number of subjects, duration of the study, types of interventions, types of comparison, types of outcome measures, the settings of the study and baseline lipid profiles. Background lipid-lowering therapy treatments and doses in each study were also recorded. For outcome measures we extracted the percent reduction in LDL-C, the mean differences and their corresponding 95% CI or standard errors (SEs) of PCSK9 inhibitors versus placebo or Ezetimibe for each lipid entity. As for safety data we extracted the number of events of interest from each study.

Quality assessment

The studies included in this review were scored by Black and Downs' checklist, where Downs's checklist comprises of 27 items for evaluating the risk of bias and the score ranges from 0 to 31.

RESULTS

Study selection

The databases generated 1567 articles from BMC, PubMed, Cochrane CENTRAL, ScienceDirect and Clinical key. 152 articles were generated from other sources including google search. After assesments of the studies, 1606 articles were excluded, of which, 1137 were abstracts only, 457 were guidelines, books, forums and 12 were study protocols. At this stage, 113 articles were assessed for duplications and availability of full text articles that lead to the final inclusion of 7 studies for this review. The small number of articles generated for the final inclusion may be attributed to the restrictions in the search strategy including the trials that were only conducted in and after 2012. This is mainly due to the conduct of Phase II and Phase III clinical trials being initiated only after 2012. However, the sample size in the included studies were large enough for a statistical and a clinically meaningful outcome interpretation.

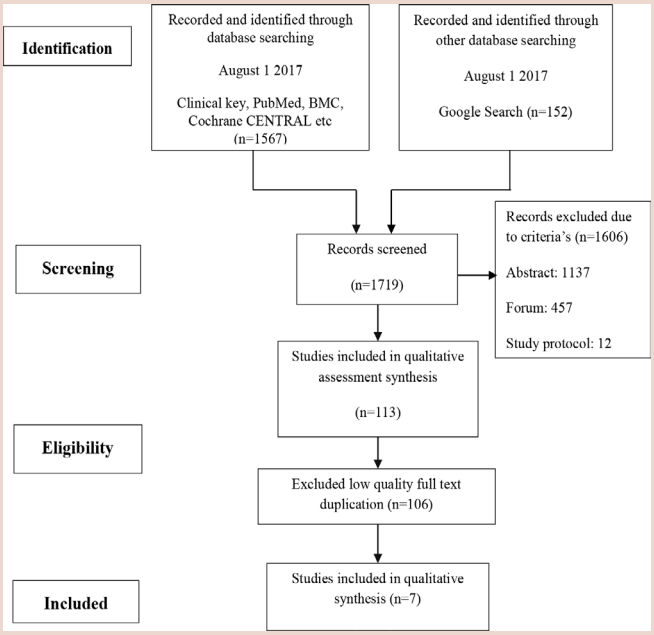

Figure 1: Scheme of selection of studies.

Table 1: Selection criteria of the studies for the review.

Inclusion criteria:	Exclusion Criteria:
• Cardiovascular disease risk • Randomised control trials phase II and beyond. • Combination with statins with or without ezetimibe • LDL-C ≥ 70mg/dl or ≥ 100mg/dl for those who have established cardiovascular disease.	• Observational studies • Analytical papers • Phase Ia studies • Mono therapy studies • Intolerance to single statin • Non-English papers

All subjects in the trials were screened for the eligibility criteria before initiation of the study and the study included subjects with a baseline statin therapy and LDL-C ≥ 70mg/dL for patients with CVD and ≥ 100mg/dL in case of CVD risk equivalents. All the baseline lipid characteristics were accounted for and the conclusions were simultaneously drawn. The study characteristics like geographical area in which study was conducted, age of subjects, sample size, selection criteria, study pool, reduction in LDL-C, percent of subjects reaching the goal of LDL-C reduction and the primary and secondary efficacy parameters are shown in Table 2.

Mean percentage change from baseline LDL-C was measured as primary efficacy parameter (Table 2) and other lipid parameters like Apo B, high density lipoprotein concentration (HDL-C), triglycerides (TGs) and very low density lipoproteins (VLDL) were considered as secondary efficacy measurements in the study.[12-16] (Table 3). Dias *et al.*[17] and Gibbs *et al.*[18] included the safety and tolerability of the drugs as their primary safety parameters in their study. They also viewed into the effect of interventional drug on the free levels of PCSK-9. Percent of subjects achieving LDL-C goal of <70mg/dL was considered as secondary efficacy parameters in the study conducted by Kiyosue *et al.*[12] and Stroes *et al.*[15] The aim of the studies included in this review was to recognise the efficacy and safety of the use of interventional drug and its influence on the lipid status of the subjects.

Table 2: Characteristics of included study and Comparison of Evolocumab with other alternatives and its mean percentage changes in LDL-C reduction.

Study Name and Region	Age (Years) and Sample size	Selection criteria	Primary and Secondary Efficacy Parameters	Study pool	Reduction in LDL-C(%)	% of subjects reaching the Goal
Kiyosue *et al.* (2016) Japan	20 -85 years 409	*Inclusion:* - age ≥20 and ≤85 years - high risk for CV events. - on a stable dose of an approved statin for ≥4 weeks before LDL- C screening *Exclusion:* - Class III or IV heart failure. - left ventricular ejection fraction < 30%, - serious cardiac arrhythmia within the last 6 months…	Primary Efficacy Parameters - mean % change from baseline in LDL-C at week 12 Secondary Efficacy Parameters -mean % change from baseline at weeks 10 and 12 in other lipids, including apolipoprotein B. -achievement of LDL-C <70 mg/dl; -Percent change from baseline in Lp(a), tri-glycerides, high-density lipoprotein cholesterol and LDL-C	Atorvastatin 20mg group: Placebo Q2W Placebo QM Evolocumab 140 mg Q2W Evolocumab 420 mg QM Atorvastatin 5mg group: Placebo Q2W Placebo QM Evolocumab 140 mg Q2W Evolocumab 420 mg QM	75.9% 66.9% 74.9% 69.9%	59% 88% 100% 100% 29% 42% 100% 100%
Gibbs *et al.* (2016) US			Primary efficacy parameters -safety and tolerability of AMG 145 Secondary efficacy Parameters -effects of AMG 145 on serum LDL-C -effect of parameters like free PCSK9, Apo-B, and lipoprotein-a levels	Placebo Evolocumab 14 mg QW Evolocumab 35 mg QW Evolocumab 140 mg Q2W Evolocumab 280mgQ2W Evolocumab 420mg QM	68.9% 63.5% 68.9%	
Stroes *et al.* (2014) multicenter, global	18 - 80 307	*Inclusion:* - not on a statin, or were able to tolerate only a low-dose statin. - Not at LDL-C goal - had a history of statin intolerance Exclusion: - recent acute coronary syndrome, - severe heart failure, a recent serious arrhythmia, - severe chronic kidney disease, - other medical comorbidities	Primary efficacy parameters -percent change from baseline in LDL-C at the mean of weeks 10 and 12 and at week 12 Secondary efficacy Parameters - change from baseline in LDL-C, - percent of patients with LDL-C <70 mg/dl, - percent change from baseline in non–HDL-C, apolipoprotein B, total cholesterol/HDL-C ratio, apolipoprotein-B/apolipoprotein-AI ratio, lipoprotein(a), triglycerides, HDL-C, and very low-density lipoprotein (VLDL-C).	Ezetimibe QD + Placebo Q2W. Evolocumab 140mg + Placebo QD. Ezetimibe QD+ Placebo QM. Evolocumab 420 mg QM + Placebo QD.	19.2% 56.1% 16.6% 55.3%	
Desai *et al.* (2014) U.S.	18 to 80 year631	*Inclusion:* - known hypercholesterolemia - on statin therapy (with or without concomitant ezetimibe *Exclusion:* - recent acute coronary syndrome, severe heart failure. - recent serious arrhythmia severe. - chronic kidney disease. - major medical comorbidities.	Primary efficacy parameter - percent change in LDL-C Secondary efficacy Parameters -absolute change in LDL-C from baseline to week 12, - percent change in non–HDL-C and ApoB from baseline to week 12, - percent change in the ratio of total cholesterol/ HDL-C and Apo B/ApoA1.	Evolocumab 70 mg Q2W Evolocumab 105 mg Q2W Evolocumab 140 mg Q2W Placebo Q2W Evolocumab 280 mg Q4W Evolocumab 350 mg Q4W Evolocumab 420 mg Q4W placebo Q4W	64% 45%	50% 72% 90% 3% 63% 65% 70% 0

Continued....

Table 2: Continued...

Study Name and Region	Age (Years) and Sample size	Selection criteria	Primary and Secondary Efficacy Parameters	Study pool	Reduction in LDL-C(%)	% of subjects reaching the Goal
Dias *et al.* (2012) 10 U.S. center	Aged ≥18 57		Primary efficacy parameters - safety and tolerability Secondary efficacy Parameters - effects of AMG 145 - Additional lipid parameters: free PCSK9, Apo-B, and lipoprotein (a).	Evolocumab 14mg, Evolocumab 35 mg SC Evolocumab 140 mg SC Evolocumab 280 mg SC Evolocumab 420 mg SC Evolocumab 140 mg + High dose statins Evolocumab 140 mg + High dose statins in HeFH Matching placebo.	24% 55% 73% 75% 63% 65% 66% 2%	
Raal *et al.* (2012) North America, Western Europe, Hong Kong, Singapore, and South Africa	18 – 75 years 168	*Inclusion:* - Men and women aged 18 to 75 years with a diagnosis of HeFH. - LDL-C ≥2.6 mmol/L (100 mg/dL) - triglycerides 4.5mmol/L (400 mg/dL) - at least 4 weeks of stable statin and other lipid- lowering therapy. Exclusion: - homozygous FH - LDL or plasmapheresis within 12 months of randomization; - heart failure Left - ventricular ejection fraction 30%; -acute or unstable cardiac events…	Primary efficacy Parameters - percentage change In LDL-C Secondary efficacy Parameters - absolute change from baseline in LDL-C at week 12, - percentage change from baseline at week 12 in non–HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio.	Placebo Q4W Evolocumab 350mg Q4W Evolocumab 420mg Q4W	1.1% 42.7% 55.2%	95%
Giugliano *et al.* (2012) USA, Canada, Denmark, Hungary, and Czech Republic	8–80 years 631	*Inclusion:* - history of hypercholesterolemia - fasting LDL-C greater than 2.2 mmol/L - on a stable dose of statin (± ezetimibe) for at least 4 weeks *Exclusion:* - Patients with severe comorbidities - taking lipid- lowering drugs other than statin or ezetimibe.	*Primary efficacy parameters* - Percentage change from baseline in LDL-C at week 12. Secondary efficacy Parameters - Absolute change from baseline in LDL-C at week 12 - The percentage changes from baseline to week 12 in concentrations of non-HDL cholesterol and apolipoprotein-B, - ratio of total cholesterol to HDL-C and apolipoprotein-B to apolipoprotein-A1 concentration.	Evolocumab 70 mg Q2W Evolocumab 105 mg Q2W Evolocumab 140 mg Q2W Evolocumab 280 mg Q4W Evolocumab 350 mg Q4W Evolocumab 420 mg Q4W	41.8% 60.2% 66.1% 41.8% 50% 50.3%	

Table 3: Comparison of Evolocumab and other alternatives with mean percentage changes in other lipid parameters.

Study	Sub groups	Non HDL-C	Apo-B	Lipoprotein (a)	Triglyceride	HDL-C	Total Cholesterol
Kiyosue *et al.* (2016)	*Atorvastatin 20mg group:* Evolocumab 140 mg Q2W	-	-60.4	-52.7	-17.2	16.9	-
	Evolocumab 140 mg Q2W	-	-56.2	-40	-16.9	10.2	-
	Atorvastatin 5mg group:	-	-65.6			13.5	-
	Evolocumab 140 mg Q2W			-50.1	-27.6		
	Evolocumab 420 mg QM	-	-57.2	-48.8	-20	15.2	-
Stroes *et al.* (2014)	Ezetimibe QD + Placebo Q2W	-	-13.7	-2.3	-	0.3	-
	Evolocumab 140 mg + Placebo QD	-	-45.9	-26.2	-	5.5	-
	Ezetimibe QD + Placebo QM	-	-11	1.6	-	1.4	-
	Evolocumab 420 mg QM + Placebo QD	-	-46.0	-23.7	-	7.2	-
Dias *et al.* (2012)	Evolocumab 14mg,	-	-19	-20	-	-15	-
	Evolocumab 35 mg SC	-	-46	-30	-	-35	-
	Evolocumab 140 mg SC	-	-53	-33	-	-46	-
	Evolocumab 280 mg SC	-	-56	-37	-	-41	-
	Evolocumab 420 mg SC	-	-50	-38	-	-41	-
	Evolocumab 140 mg + High dose statins	-	-48	-45	-	-36	-
	Evolocumab 140 mg + High dose statins inHeFH	-	-46	-50	-	-41	-
	Matching placebo.	-	-4	-4	-	-2	-
Raal *et al.* (2012)	Placebo Q4W	2.5	2.9	4.1	9.4	2.3	2.9
Giugliano *et al.* (2012)	Evolocumab 70 mg Q2W	-38.4	-34.7	-	-18.1	6.9	-26.2
	Evolocumab 105mgQ2W	- 55.4	-50.1	-	-24.9	6.6	-39.4
	Evolocumab 140 mg Q2W	-61.4	-56.4	-	-32.7	8.1	-42.5
	Evolocumab 280 mg Q4W	-37.8	-34.4	-	-13,4	1.6	-26.9
	Evolocumab 350 mg Q4W	-45.8	-40.8	-	-13.7	5.5	-32.6
	Evolocumab 420 mg Q4W	-47.6	-42	-	-19.4	4.5	-32

LDL-C Reduction

In the study conducted by Kiyosue *et al.*[12] among the study population who are treated with Evolocumab showed LDL-C reduction in 67% to 76% patients when compared with placebo. Apart from the LDL-C reduction, the treatment group with Evolocumab, showed the mean (standard error) treatment differences for non LDL-C lipids at the 12th week was 56% (2%) to 66% (2%) for apolipoprotein B, 10% (3%) to 17% (3%) for HDL-C and 40% (5%) to 53% (6%) for Lp(a) for intervention versus the placebo.[12]

In a randomized placebo controlled study conducted by Dias *et al.*[17] when Evolocumab was administered, there was significant dose dependent reduction in LDL-C levels of 81% from baseline, ($p \leq 0.001$) versus placebo. And at the end of dosing interval, there was 75% reduction ($p \leq 0.001$). Moreover, the LDL-C reduction observed in the high-dose statin was comparable to low to moderate dose statin group. Furthermore, Evolocumab also contributed to significant decrease in ApoB by 59% as compared to placebo ($p < 0.001$). There was also a reduction of 27% LDL-C (35 mg QW6, $p \leq 0.033$) compared to placebo.[1]

In the phase two, double blind, placebo controlled study conducted by Desai *et al.*[14] it was found that the standard deviation (SD) of the LDL-C levels for subjects receiving Evolocumab 140 mg were 47±30 mg/dl and 59±29 mg/dl for every 2 weeks at the 12th week. Hitherto, all the subsequent doses of Evolocumab resulted in significant increase in number of subjects who attained the recommended levels of LDL-C, that is <70 mg/dl at 12th week ($p < 0.001$). Furthermore, each of Evolocumab doses caused significant achievement of non–HDL-C <100 mg/dl and ApoB <80 mg/dl ($p < 0.001$).[14] The changes in other lipid parameters are represented in Table 3.

Similarly as per the study conducted by of Stroes *et al.*[15] which is a phase three randomized placebo controlled study, the patients had baseline LDL-C of 193±59mg/dl and when Evolocumab 140 mg Q2W was administered for the treatment group it presented significant mean percent reductions of 56.1% (95% CI: 59.7% to 52.5%) from the baseline at weeks 10 and 12. In addition, Evolocumab 420 mg QM resulted in reductions of 55.3% (95% CI: 58.3% to 52.3%) alternative to the differences against Ezetimibe with 36.9% (95% CI: 42.3% to 31.6%) and 38.7% (95% CI: 43.1% to 34.3% $p < 0.001$) respectively. In terms of secondary lipid profile when compared with Ezetimibe, significant reductions were demonstrated by Evolocumab for lipoprotein (a), ApoB and non HDL-C ($p < 0.001$).[15]

In a phase two, global, multi-center, double-blind, placebo-controlled trial was conducted by Raal *et al.*[16] the Mean SE absolute values pertaining to LDL-C at the 12th week for Evolocumab 350 mg was 2.3 (0.2), for Evolocumab 420 mg was 1.7 (0.1), and for placebo was 4.2 (0.2) mmol/L (89.9 [6.4], 65.1 [4.0], and 162.5 [7.3] mg/dL).[16] In the study conducted by Gibbs *et al.*[17] where Evolocumab doses of 140 mg Q2W, 280 mg QM, and 420 mg QM were administered, reduced the LDL-C of 68.9%, 63.5%, and 68.9%, respectively from the baseline. Percent of LDL-C reduction from baseline is represented in Table 2.

Evolocumab produced a greater margin of LDL-C reductions when compared to placebo in all the studies irrespective of statin dose. With various doses of Evolocumab, Kiyosue *et al.*[12] presented an outcome with mean of 71.9% reductions in the LDL-C from baseline, while other studies[13-18] showed 60.1, 54.4, 55.7, 51.7, 48.95 and 67.1 LDL-C reduction respectively. Dias *et al.*[17] Desai *et al.*[14] Stroes *et al.*[15] Giugliano *et al.*[13] Raal *et al.*[16] and Gibbs *et al.*[18]showed 60.1%, 54.4%, 55.7%, 51.7%, 48.95% and 67.1% LDL-C reduction, respectively. Resultant pooled mean of the 7 studies outline 58.5% reductions in the LDL-C. The extent of LDL-C reductions by statins is well accepted around 15%.[1] The efficacy of PCSK9 inhibitors on lowering of LDL-C has a major role in both treatment and prevention of further cardiovascular events. Furthermore, the combination of statins and Evolocumab resulted in much higher LDL-C reductions and thereby an optimised lipid management.[19-27]

LDL-C goal attainment

Number of patients achieving LDL-C goals was consistently higher in the interventional arm than the control, with no correlation between statin dose and the percentage of patients reaching the target LDL-C. However the percent reduction in LDL-C showed a significant relationship to statin dose.

Safety summary

The safety and adverse effects profile of the studies are presented in Table 3. In the study by Kiyosue *et al.*[12] the incidence of adverse events of placebo was similar to that of interventional group. The rate of discontinuation and adverse events across the placebo and the interventional groups were also found to be quite similar, there by indicating a good aspect of tolerability of the dosing regimens. Furthermore, serious adverse events (SAEs) were found infrequent in both the groups.[12]

Moreover, in the study by Desai *et al.*[14] it was found that the incidence of injection-site reactions was reported by only 2% from the subtotal of 629 subjects. There were no reports of patients developing any anti Evolocumab antibody, neutropenia or vasculitis.[14]

However, in the study by Dias *et al.*[17] SAEs or adverse events leading to discontinuation were not observed. Besides, adverse events considered treatment related were estimated as 23% and 14% of subjects receiving Evolocumab and placebo respectively.[18] Additionally, for the study undertaken by Stroes *et al.*[15] the incidence of adverse events that led to drug discontinuation was 8% for Evolocumab and 13% in Ezetimibe subjects.[15]

As a whole, the incidence of TEAEs, TESAEs, and TEAEs leading to death or discontinuation and injection site reactions are listed in Table 4. In conclusion, it is quite evident that Evolocumab has a good safety margin and high range of tolerability.

DISCUSSION

This review emphasizes on the hypothesis that by considering Evolocumab as add on therapy to statins, the LDL-C lowering capacity of statins are furthermore enhanced. In spite of the great history of success with statin therapy in the treatment and prevention of cardiovascular events, owing the increased rate of therapeutic failure, an additional approach is required. Generally, a huge number of patients are unable to reach their target LDL-C i.e.<70mg/dL, initially. Moreover, patients with HoFH or HeFH require extra therapies in addition to standard for further reductions in LDL-C. Furthermore, a subset of patients were found to be intolerant to statin therapy resulting into therapy related adverse events such as myopathy, myalgia and hepatotoxicity.[28-29] Therefore, it is relevant to consider a novel therapeutic approach through PCSK9 inhibition.

Furthermore, there is long term data required regarding the safety aspects of Evolocumab. However, most of the clinical studies had a mean duration of 12 weeks, which is not sufficient for the safety confirmation. Evolocumab use for 12 weeks was safe and well tolerated by majority of the subjects involved in the included studies while a small percent of the patients were discontinued for the therapy due to either the patient's particular reasons including unwillingness to continue the study or by the decision of the investigator when seen appropriate. The major common side effects that have been listed include injection-site reactions, urinary tract infections, nasopharyngitis and headache.[12-18]

The outcome of trials of long duration would also amplify the immune response to the therapy, given that the possibility of developing anti-drug

Table 4: Safety and adverse event outcomes of Evolocumab.

	TEAEs	TESAEs	TEAE leading to death	TEAE leading to discontinuation	Injection site reactions.
Kiyosue *et al.* (2016) (N = 202)	94 (46.5%)	1 (0.49%)	0 (0%)	0 (0%)	5 (2.47%)
Gibbs *et al.* (2016)	-	-	-	-	-
Stroes *et al.* (2014) (N = 205)	135 (65.8%)	6 (2.9%)	0 (0%)	17 (8.2%)	6 (2.9%)
Desai *et al.* (2014) (N = 229)	20 (8.7%)	6 (2.6%)	0 (0%)	0 (0%)	0 (0%)
Dias *et al.* (2012) (N = 43)	10 (23%)	0 (0%)	0 (0%)	0 (0%)	2 (4.6%)
Raal *et al.* (2012) (N = 111)	69 (62.1%)	2 (1.8%)	0 (0%)	2 (1.8%)	7 (6.3%)
Giugliano *et al.* (2012) (N = 474)	39 (8.2%)	11 (2.3%)	0 (0%)	0 (0%)	8 (1.6%)

antibodies which may in turn lead to the loss of therapeutic effect. Current studies have demonstrated only about 0.1% of the patients presenting with anti-drug antibodies however without the loss of therapeutic effect.[30-31]

The impact of PCSK9 inhibitors on other lipid parameters has also been studied. While significantly resulting in the reduction of LDL-C, it was also seen to consequently impact the levels of HDL-C, TG, very low density lipoprotein, and Lp(a).[32-33] The involvement of Evolocumab in day-to-day care of patients would definitely lead to practical modifications in current clinical practice. The possible targets for Evolocumab therapy include patients intolerant to statin, patients with familial history and those patients in need of additional therapy to reach their target LDL-C levels.

One of the most debatable issue in implementation of Evolocumab in current clinical practice remains in defining the criteria for the patients to be claimed with high cardiovascular risk, which consequently renders the need of further reductions in LDL-C and thus the combination of PCSK9 inhibitors and statins.[34]

For those patients who fail to reach optimal LDL-C targets on statin therapy, the reason is predominantly related to statin intolerance.[26,17] PCSK9 inhibitors is ideal approach for lipid lowering, as the extent of LDL-C reduction with it is much greater than the existing approaches.[22,35] It is evident that statins are responsible for increased expression of PCSK9.[30]

Similarly, in the study done by Sullivan *et al.*[36] there was only 40.8% of reduction in LDL-C with Evolocumab 280 mg QM monotherapy while in a study undertaken by Desai *et al.*[14] there was 45% reductions in LDL-C for patients with Evolocumab 280 mg QM on a stable statin therapy. Likewise, in a study by Robinson *et al.*[29] it was identified that Evolocumab added to moderate or high intensity statin therapy resulted in additional LDL-C lowering. On the contrary, Atorvastatin 80 mg daily with Evolocumab QM, resulted in 60.1% LDL-C reduction whereas atorvastatin 10 mg with Evolocumab QM led to a reduction of 80.1% in LDL-C which is far more greater than that combined with high intensity statins. Additive evidence of the same was shown in the study concluded by Dias *et al.*[17] where Evolocumab 140 mg given with high dose statins resulted in only 65% of LDL-C reduction as compared to 73% reduction in Evolocumab 140 mg and low to moderate dose statins. These set of evidences highly attributes to the fact that statins elevate the blood PCSK9 levels and thus causing lesser degree of LDL-C reduction.

While considering when to add PCSK9 inhibitor, high relevance is seen in patients with ASCVD, with major risks for ASCVD and LDL-C ≥140 mg/dL or ≥100mg/dL with high risk for developing ASCVD.[37] Additionally, as per Boccara *et al.*[38] in applications of polypharmacy and to prevent mortalities in events of acute cardiovascular events, it is substantially associated with issues of adherence.

The costs for PCSK9 inhibitors will be approximated to billions of dollars for about 10 million patients,[34] and with the rising incidence of CVD, the costs is estimated to around 1 trillion by the year of 2030 in the United States. However, the cost to society is assumed at a 50% CVD risk reduction with the use of PCSK9 inhibitor therapy.[33] Nonetheless, the need of a novel method to improvise and personalize clinical decision making and for the assessment of potential adverse effects in the light of present epidemiological incidence is a must.[4,39-40]

Various biological pathways that underline the lipid profile are researched for a better understanding and therapeutic approach. According to a study, the relationship between PCSK9 and lipoprotein sub- fractions was associated with the male patients but not with females, suggesting that the interaction of PCSK9 with lipoprotein sub-fractions may be attributed as a novel mechanism including gender disparity.[23] Additionally, there was no association between plasma PCSK9 and apo B-48 levels.[32]

Limitations of the review were that there are very limited number of available trials, and the unclear specification of statin intolerance in some of the papers. The clinical trials concerning evolocumab were only conducted in and after 2012 rendering only limited number of studies that were published. Moreover, very limited data is present on the post marketing outcome and analysis. Additionally the data on baseline statin dose was unclear in some of the studies.

CONCLUSION

In this review, the addition of Evolocumab to baseline statin therapy led to a significant reduction in LDL-C in heterozygous familial hypercholesterolemia and ASCVD. However it was also noted that low dose statins with Evolocumab resulted in considerably higher reductions in LDL-C as compared to high dose statins combination with Evolocumab. Further trials are needed to assess this variability to conclude a better approach for the addition of Evolocumab with a baseline statin therapy. Moreover, only limited literatures are available to support this conclusion, there is a drastic need for further research emphasizing on RCTs

inlcuding evolocumab compared to placebo or other lipid lowering therapies for LDL-C reduction.

ACKNOWLEDGEMENT

The authors wish to thank JSS Academy of Higher Education and Research, Mysuru for providing the facilities and support to conduct Workshop on Scientific Writing by the Department of Pharmacy Practice.

CONFLICT OF INTEREST

Authors of this review do not have any conflict of interest.

ABBREVIATIONS

ApoB: Apolipoprotein B; **ASCVD:** Atherosclerotic Cardiovascular Disease; **ARH:** Autosomal Recessive Hypercholesterolemia; **BMC:** BioMed Central; **EMEA:** European Medicines Agency; **FDA:** Food and Drug Administration, USA; **HeFH:** Heterozygous Familial Hypercholesterolemia; **HDL-C:** High Density Lipoprotein Concentration; **HoFH:** Homozygous Familial Hypercholesterolemia; **LDL-C:** Low Density Lipoprotein concentration; **PCSK9:** Proprotein Convertase Subtilisin/Kexin Type 9; **TEAEs:** Treatment Emergent Adverse Events; **TESAEs:** Treatment Emergent Serious Adverse Events; **TGs:** Triglycerides; **VLDL:** Very Low Density Lipoproteins.

REFERENCES

1. Stone NJ, Robinson J, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. J Am Coll Cardiol. 2014;63(25): 2889-934.
2. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, *et al.* Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. Circulation. 2011;123(20):2292-333.
3. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an Antibody to PCSK9 in Primary Hypercholesterolemia. N Engl J Med. 2012;367(20):1891-900.
4. Quispe R, Hendrani A, Elshazly MB, Michos ED, McEvoy JW, Blaha MJ, *et al.* Accuracy of low-density lipoprotein cholesterol estimation at very low levels. BMC Med. 2017;15(1):83.
5. Lambert G, Sjouke B, Choque B, Kastelein JJP, Hovingh GK. The PCSK9 decade. J Lipid Res. 2012;53(12):2515-24.
6. Werzbick A, Grant P. Drugs for hypercholestrolaemia - From statins to pro-protein convertase subtilisin kexin 9 (PCSK9) inhibition. Clin Med J R Coll Physicians London. 2016;16(4):353-7.
7. Lagace TA. PCSK9 and LDLR degradation: Regulatory mechanisms in circulation and in cells. Curr Opin Lipidol. 2014;25(5):387-93.
8. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, *et al.* Anti-PCSK9 monotherapy for hypercholesterolemia: The MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23): 2531-40.
9. Chaudhary R, Garg J, Shah N, Sumner A. PCSK9 inhibitors: A new era of lipid lowering therapy. World J Cardiol. 2017;9(2):76-91.
10. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, *et al.* Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events. N Engl J Med. 2015;372(16):1500-9.
11. Rosenson RS, Jacobson TA, Preiss D, Djedjos CS, Dent R, Bridges I, *et al.* Efficacy and Safety of the PCSK9 Inhibitor Evolocumab in Patients with Mixed Hyperlipidemia. Cardiovasc Drugs Ther. 2016;30(3):305-13.
12. Kiyosue A, Honarpour N, Kurtz C, Xue A, Wasserman SM, Hirayama A. A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk. Am J Cardiol. 2016;117(1):40-7.
13. Giugliano, Robert P, Desai N, Kohli P, Rogers WJ, Somaratne R, *et al.* Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-raning, phase 2 stud. Lancet. 2012;380(9858):2007-17.
14. Desai NR, Giugliano RP, Zhou J, Kohli P, Somaratne R, Hoffman E, *et al.* AMG 145, a monoclonal antibody against PCSK9, facilitates achievement of national cholesterol education program-adult treatment panel III low-density lipoprotein cholesterol goals among high-riskpatients: An analysis from the LAPLACE-TIMI 57 trial (LDL-C). J Am Coll Cardiol. 2014;63(5):430-3.
15. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, *et al.* Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: The GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2541-8.
16. Raal F, Scott R, Somaratne R, Bridges I, Li G, Wasserman SM, *et al.* Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: The reduction of LDL-Cwith PCSK9 inhibiti. Circulation. 2012;126(20):2408-17.
17. Dias CS, Shaywitz AJ, Wasserman SM, Smith BP, Gao B, Stolman DS, *et al.* Effects of AMG 145 on low-density lipoprotein cholesterol levels: Results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. J Am Coll Cardiol. 2012;60(19):1888-98.
18. Gibbs JP, Doshi S, Kuchimanchi M, Grover A, Emery MG, Dodds MG, *et al.* Impact of Target-Mediated Elimination on the dose and regimen of Evolocumab, a human monoclonal antibody against Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). J Clin Pharmacol. 2017;57(5):616-26.
19. Reiner Ž, Catapano AL, Backer GD, Graham I, Taskinen MR, Wiklund O, *et al.* ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2011;32(14):1769-818.
20. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, *et al.* Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: Guidance for clinicians to prevent coronary heart disease. Eur Heart J. 2013;34(45):3478-90.
21. Xanthopoulou I, Davlouros P, Siahos S, Perperis A, Evangelia Z, Alexopoulos D. First-line treatment patterns and lipid target levels attainment in very high cardiovascular risk outpatients. Lipids Heal Dis. 2013;12(1):170.
22. Perry RJ, Samuel VT, Petersen KF, Shulman GI, Haven N, Haven N. PCSK9 inhibition to reduce cardiovascular disease risk: recent findings from the biology of PCSK9. HHS Public Access. 2015;510(7503):84-91.
23. Xu R-X, Li S, Zhang Y, Li X-L, Guo Y-L, Zhu C-G, *et al.* Relation of plasma PCSK9 levels to lipoprotein subfractions in patients with stable coronary artery disease. Lipids Health Dis. 2014;13(1):188.
24. Daniell H. Residual Cardiovascular Risk Despite Optimal LDL-Cholesterol Reduction with Statins: The Evidence, Etiology, and Therapeutic Challenges. NIH Public Access. 2012;14(1):1-10.
25. Urban D, Pöss J, Böhm M, Laufs U. Targeting the proprotein convertase subtilisin/kexin type 9 for the treatment of dyslipidemia and atherosclerosis. J Am Coll Cardiol. 2013;62(16):1401-8.
26. Shah P, Glueck CJ, Goldenberg N, Min S, Mahida C, Schlam I, *et al* . Efficacy, safety, Low density lipoprotein cholesterol lowering, and calculated 10-year cardiovascular risk reduction of alirocumab and evolocumab in addition to maximal tolerated cholesterol lowering therapy: a post-commercialization study. Lipids Health Dis. 2017;16(1):19.
27. Hassan M. OSLER and ODYSSEY LONG TERM: PCSK9 inhibitors on the right track of reducing cardiovascular events. Glob Cardiol Sci Pract. 2015;2015(2):20.
28. Nissen SE, Dent-Acosta RE, Rosenson RS, Stroes E, Sattar N, Preiss D, *et al.* Comparison of PCSK9 Inhibitor Evolocumab vs Ezetimibe in Statin-Intolerant Patients: Design of the Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects 3 (GAUSS-3) Trial. Clin Cardiol. 2016;39(3): 137-44.
29. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, *et al.* Effect of evolocumab or ezetimibe added to moderate- Or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: The LAPLACE-2 randomized clinical trial. J Am Med Assoc. 2014;311(18):1870-82.
30. Seidah NG, Awan Z, Chrétien M, Mbikay M. PCSK9: A key modulator of cardiovascular health. Circ Res. 2014;114(6):1022-36.
31. Farnier M. PCSK9: From discovery to therapeutic applications. Arch Cardiovasc Dis. 2014;107(1):58-66.
32. Drouin-Chartier JP, Hogue JC, Tremblay AJ, Bergeron J, Lamarche B, Couture P. The elevation of plasma concentrations of apoB-48-containing lipoproteins in familial hypercholesterolemia is independent of PCSK9 levels. Lipids Health Dis. 2017;16(1):119.
33. Glueck CJ, Shah P, Goldenberg N, Prince M, Lee K, Jetty V, *et al.* Eligibility for PCSK9 treatment in 734 Hypercholesterolemic patients referred to a regional cholesterol treatment center with LDL cholesterol ≥70 mg/dl despite maximal tolerated cholesterol lowering therapy. Lipids Health Dis. 2016;15(1):1-6.
34. Shah P, Glueck CJ, Jetty V, Goldenberg N, Rothschild M, *et al.* Pharmacoeconomics of PCSK9 inhibitors in 103 hypercholesterolemic patients referred for diagnosis and treatment to a cholesterol treatment center. Lipids Health Dis. 2016;15(1):1-9.
35. Shen L, Peng H, Xu D, Zhao S. The next generation of novel low-density lipoprotein cholesterol-lowering agents: Proprotein convertase subtilisin/kexin 9 inhibitors. Pharmacol Res. 2013;73(1):27-34.
36. Sullivan D, Olsson AG, Scott R, Jae B, Xue A, Gebski V, *et al.* Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. J Am Med Assoc.

2012;308(23):2497-506.
37. Pecin I, Hartgers ML, Hovingh GK, Dent R, Reiner E. Prevention of cardiovascular disease in patients with familial hypercholesterolaemia: The role of PCSK9 inhibitors. Eur J Prev Cardiol. 2017;24(13):1383-401.
38. Boccara F, Dent R, Ruilope L, Valensi P. Practical considerations for the use of Subcutaneous treatment in the management of dyslipidaemia. Adv Ther. 2017;38(8):1876-96.
39. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, *et al*. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 - Executive Summary. J Clin Lipidol. 2014;8(5):473-88.
40. Colletti A, Derosa G, Cicero AF. Retargeting the management of hypercholesterolemia — Focus on evolocumab. Ther Clin Risk Manag. 2016;12(1):1365-76.

Cite this article : Basutkar RS, Tsundue T, Siva H, Durai R, Ponnusankar S. Evolocumab in Combination with Statins for CVD Risk Reduction: An Evidential Review. J Cardiovasc Disease Res. 2018;9(2):45-53.