Original Article

Safety and efficacy of alirocumab: A meta analysis of 12 randomized controlled trials

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Abstract

Background and Objective: Hypercholesterolemia is one of the major risk factor for atherosclerotic coronary heart disease, especially coronary heart disease. Most effective class of medications for prevention of cardiovascular events and LDL-C reduction are the statins. Approximately only one fourth of these high risk patients had achieved LDL-C levels <70 mg/dL with statins. Monoclonal antibody targeting PCSK9 is a novel class of drug used in the treatment of Hypercholesterolemia. Alirocumab is one such human monoclonal antibody directed against PCSK9. Binding of PCSK9 to the LDL-R on the hepatocytes promotes LDL-R degradation. Inhibition of PCSK9 binding to LDL-R leads to increased number of LDL-Rs to clear LDL, thus decreasing LDL-C levels. The purpose of this systematic study is to assess the safety and efficacy of Alirocumab in adults with hypercholesterolemia and Familial hypercholesterolemia. **Materials and Methods:** We searched Medline, PubMed Central database, Google scholar, EBSCO, Wiley library, conference proceedings and Clinical trials.gov registry through March 2017. Phase 3 randomized, controlled trials (RCTs) using Alirocumab in adults with hypercholesterolemia and Familial Hypercholesterolemia were selected. **Results:** In twelve RCTs comprising of 6019 patients included in the meta-analysis, significant favorable changes in LDL-C and HDL-C were found. **Limitations:** Results were derived from study level data rather than patient level data. **Conclusions:** Alirocumab substantially reduced the LDL-C level by over 50 %, increased the HDL-C level, and resulted in favorable changes in other lipids.

Keywords: Alirocumab, dyslipidemia, familial hypercholesterolemia, low density lipoprotein (LDL) cholesterol, PCSK9, PCKS9 inhibitors

Introduction

The burden of atherosclerotic cardiovascular disease (ASCVD) has been on increase in developing countries.[1-3] Hypercholesterolemia is one of the major risk factor for ASCVD, especially coronary heart disease (CHD).[4-6]

Hyperlipidemia is one of the major causes of atherosclerosis as well as of atherosclerosis-induced conditions. This atherosclerosis-induced condition includes CHD, ischemic cerebrovascular disease, and peripheral vascular disease (PVD).[7] For prevention of acute coronary syndromes (ACS), therapy is reduction of plasma low density lipoprotein cholesterol (LDL-C) reduction.[8]

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Irrespective of LDL-C level prior to the commencement of therapy, reduction in LDL-C with statins of 1 mmol/l (39 mg/dl) have been found to decrease in overall mortality by 12%, in incidence of strokes by 17%, and in coronary mortality by 19%.[9] Data collected from numerous animal, epidemiologic, genetic, and clinical studies have demonstrated direct relationship between LDL-C levels and CV risk and reduction of LDL-C levels to reduced CV risk. For every 38.6 mg/dL reduction, there has been approximately 22% reduction in major CV events to mean LDL-C levels as low as approximately 50 mg/dL. LDL-C lowering has been validated surrogate marker for cardiovascular benefit.[10]

According to American College of Cardiology/American Heart Association (ACC/AHA) guidelines, irrespective of baseline LDL-C level, use of intensive statin therapy in all high CV risk

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patients should be targeted to achieve ≥50% LDL-C reduction.[6] As per the recommendations of National Lipid Association, LDL-C level should be targeted to less than 100 mg/dL for high CVD risk subjects and less than 70 mg/dL for very high CVD risk subjects.[11] Most effective class of medications for prevention of cardiovascular events and LDL-C reduction are the statins.[12]

Statins, being the most potent agent, are the first line drugs for the treatment of dyslipidemia. Among antidyslipidemic drugs, statins are the most frequently prescribed drugs. Statins have found to reduce CV risk among all the risk factor categories.[13] Patients with familial hypercholesterolemia and individuals at high risk of ASCVD require substantial reduction of LDL-C level. For this substantial reduction of LDL-C level new, highly effective lipid modifying therapy is required.[14]

According to the reports of a cross-sectional survey, about 2/3rd of high risk CV patients on statins for more than 90 days have not achieved LDL-C levels <100 mg/dL. Approximately only 1/4th of these high risk patients had achieved LDL-C levels <70 mg/dL. As per one of a European study, fewer than half of the dyslipidemic patients achieved LDL-C levels <100 mg/dL with available lipid lowering drugs. Approximately 80% of heFH patients do not achieve LDL-C levels less than 100 mg/dL with statin monotherapy. 10-11% significant residual risk with statin therapy has been a cause of concern.[15]

Adherence to these guidelines, available therapeutic options are unable to provide adequate efficacy for eliminating the surplus CV risk attributable to their LDL-C level.[16] There is considerable proportion of high risk patients who are unable to achieve optimal LDL-C reduction. There is significant residual risk of ACS even after intensive statin therapy.[8] Factors responsible for failure of statins to reach target LDL-C levels are submaximal dosing, non-adherence to therapy due to ADRs, pharmacologic interactions with other drugs and only upto 6% additional reduction in LDL-C with doubling of the dose.[17]

Non-statin therapies are recommended for high risk patients who are having less-than-anticipated response to statins, who are having completely statin intolerance or who are unable to tolerate recommended intensity of statins.[6] Approximately 10-15% of patients treated with high-intensity statins exhibit some degree of intolerance with a fraction of patients discontinuing therapy due to muscle pain or weakness.[18] There are limited therapeutic options for these patients which using a less potent statin or starting with a lower dose, or employing non-statin therapy. These options often do not provide sufficient LDL-C lowering in patients with statin intolerance. Patients unable to take statins require a new treatment option to achieve their target LDL-C reduction goals.[10] PCSK9 has key role in regulation of cholesterol homeostasis. PCSK9 bind to LDL-R and promote their degradation. Degradation of LDL-R reduces LDL uptake resulting in increased level of LDL-C concentrations.[19] Alirocumab is a human monoclonal antibody against PCSK9. Binding of PCSK9 to the LDL-R on the hepatocytes promotes LDL-R degradation. LDL-R are responsible for clearing circulating LDL, thus reduction in LDL-R levels results in higher LDL-C levels. Inhibition of PCSK9 binding to LDL-R leads to increased number of LDL-R to clear LDL, thereby decreasing LDL-C levels.[10]

Alirocumab has demonstrated significant reductions in LDL-C along with favorable changes in other lipid parameters related to cardiovascular risk. Alirocumab was approved by FDA on July 24, 2015. The physiological role of PCSK9 and its therapeutic potential in cholesterol metabolism is being explored. Analysis of efficacy and safety outcomes on alirocumab on lipid profiles are either absent or not uniformly consistent, therefore, in this study we carried out meta-analysis of RCTs to investigate the efficacy and safety of alirocumab with respect to their effects on clinical outcomes.

Methods

Data sources and literature search

We sought to identify all randomized controlled trials (RCTs) evaluating the efficacy of alirocumab. We searched EMBASE, PubMed, Google Scholar, Clinical Trial Results (www.clinicaltrialresults.org), the PCSK9 Education and Research Forum (www.pcsk9forum.org), and the American College of Cardiology Web site (www.cardiosource.com) and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to Mar 2017, using the following search terms and key words: Alirocumab, PCSK9 inhibitors, RCTs, Hypercholesterolemia, Dyslipidemia. Citations were screened at the title and abstract level, and retrieved as full reports if they were considered relevant [Figure 1].

Study selection

The main inclusion criterion was a phase 3 RCT comparing alirocumab with no alirocumab in adults with hypercholesterolemia and Familial hypercholesterolemia (HeFH), with clinical outcomes reported. No restrictions on language, follow-up, or study size were applied. The doses of alirocumab that had been used in phase 3 RCTs were selected for comparisons. Studies were included if they were Phase III RCTs; evaluated the efficacy of the alirocumab, reported mean differences with corresponding confidence intervals (CIs) or provided data necessary to calculate such. We did not restrict the type of study populations. We excluded studies which were not randomized, and studies using other anti-PCSK9 antibodies, such as evolocumab, bococizumab, or PCSK9 inhibitors such as small interfering RNA because of the limited number of trials published regarding these PCSK9 inhibitors.

Outcomes

Primary efficacy endpoints were percent and absolute reductions in LDL-C and high-density lipoprotein (HDL) cholesterol levels following alirocumab treatment after 24 weeks. Secondary efficacy end points were percent changes from baseline in total cholesterol (TC), HDL-C, Non HDL-C, Triglycerides (TG), lipoprotein (a), Apo A, and Apo B after 24 weeks.

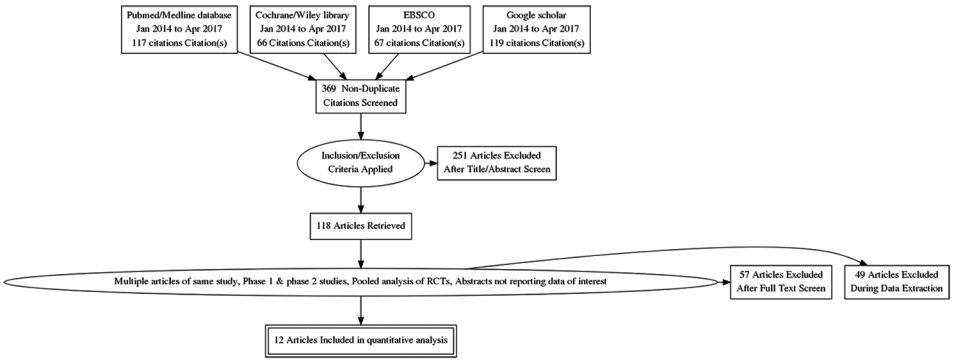

Figure 1: PRISMA summary of evidence search and selection

Data extraction and quality assessment

Data were extracted by two reviewer (RM and AS) independently, using standardized data extraction form. Third reviewer (MR) checked the data if/when there were disagreement.

The following information was extracted: trial name/first author, year of publication, number of patients, age, gender, diabetes mellitus, coronary heart disease (CHD), and all lipid profiles at baseline. Patient profile and background lipid-lowering therapy, treatments and doses in each study were also recorded. For safety endpoints, we extracted the number of events of interest and total number of patients in each group. For efficacy outcomes, as a priority, we extracted the mean differences and their corresponding 95% CIs or standard errors (SEs) of anti-PCSK9 antibody versus placebo or ezetimibe for each lipid items. Alternatively, mean changes and 95% CIs (or SEs) from baseline after either anti-PCSK9 antibody or placebo (or ezetimibe) treatments were extracted, thereafter mean differences of anti-PCSK9 antibody versus controls were calculated.

Quality assessment

We followed the Cochrane Collaboration's tool to assess the risk of bias of included trials. Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), in- complete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias were included in the assessment independently performed by two reviewers (RM and AS).

Statistical analysis

For all efficacy outcomes, the mean differences following anti-PCSK9 treatment versus placebo or ezetimibe were pooled across studies using the random-effects model. Comparisons of anti-PCSK9 antibodies with placebo or ezetimibe were performed separately and stratified by dosages of antibodies [Table 1]. Trials in which the endpoint was not detected in any of the treatment groups were excluded in the analysis of that endpoint. For studies in which only one of the groups had no event of interest, the estimate of treatment effect and its confidence interval were calculated after adding 0.5 to each cell of the 2×2 table for the trial.[10,11] We used the statistic to assess the consistency across studies, with 25%, 50%, and 75%, indicating low, moderate, and high degrees of heterogeneity respectively. Sensitivity analyses were carried out by omitting one study at one time to evaluate the consistency of the results.

Results

Primary clinical end points

All-cause mortality

Eleven RCTs with a total of 5916 patients were included in the analysis of all-cause mortality. Overall, there was a statistically significant reduction in mortality with use of alirocumab compared with no alirocumab treatment; the respective mortality rates were 0.31% (19 of 6187 patients) and 0.53% (21 of 3971 patients) (OR, 0.45 [95% CI, 0.23 to 0.86]; $P = 0.015$; heterogeneity $P = 0.63$; $I^2 = 0\%$). No inconsistency was detected across trials ($I^2 = 0\%$). The analysis that was adjusted for follow-up showed the consistency of the results (OR, 0.48 [CI, 0.27 to 0.85]; $P = 0.010$; heterogeneity $P = 0.68$; $I^2 = 0\%$). The sensitivity analysis that was stratified by comparator (placebo or ezetimibe) also supported the results.

Cardiovascular mortality

Eleven RCTs comprising 5916 patients were included in the analysis of cardiovascular mortality. There was a statistically no significant reduction in cardiovascular mortality with use of PCSK9 antibodies compared with no anti-PCSK9 treatment; the respective cardiovascular mortality rates were 0.19% (12 of 6187 patients) and 0.33% (13 of 3972 patients) (OR, 0.50 [CI, 0.23 to 1.10]; $P = 0.084$; heterogeneity $P = 0.78$; $I^2 = 0\%$). The analysis that was adjusted for follow-up showed the consistency of the results (OR, 0.49 [CI, 0.23 to 1.07]; $P = 0.070$; heterogeneity $P = 0.79$; $I^2 = 0\%$). The analysis that was stratified by comparator (placebo or ezetimibe) also supported the results.

Secondary safety end points myocardial infarction and unstable angina

Ten RCTs with a total of 5195 patients reported data on myocardial infarction. Treatment with PCSK9 antibodies resulted in a statistically significant reduction in myocardial infarction

compared with no anti-PCSK9 treatment; rates were 0.58% (19 of 3289 patients) and 1% (19 of 1906 patients), respectively (OR, 0.49 [CI, 0.26 to 0.93]; $P = 0.030$; heterogeneity $P = 0.45$; $I^2 = 0\%$). The analysis that was adjusted for follow-up showed the consistency of the results (OR, 0.49 [CI 0.26 to 0.93]; $P = 0.030$; heterogeneity $P = 0.53$; $I^2 = 0\%$). The analysis that was stratified by comparator (placebo) also supported the results.

6 RCTs including a total of 3894 patients provided data on unstable angina. The rates were similar between the 2 groups: 0.04% (1 of 2515 patients) who received PCSK9 antibodies and 0.08% (1 of 1379 patients) who did not receive PCSK9 antibodies (OR, 0.61 [CI0.06 to 6.14]; $P = 0.676$; heterogeneity $P = 0.34$; $I = 0\%$). The analysis was adjusted for follow-up for the consistency of the results (OR, 0.51 [CI, 0.05 to 4.86]; $P = 0.56$;

Efficacy end points

LDL cholesterol

12 studies comprising of 6019 patients were included in the analysis of LDL-C [Table 2 and Figure 2]. Overall, a reduction in LDL-C levels of 52% was observed with use of alirocumab compared with no PCSK9 antibody. With alirocumab reduction in LDL-C level was -52.37% [CI, - 59.26 to -45.47]; $P < 0.001$). A similar reduction in LDL values was found in placebo controlled trials (MD, -55.58% [CI, -58.87% to -52.28%]; $P < 0.001$) and in ezetimibe-controlled trials (MD, 49.17% [CI, --53.17 to -45.17%]; $P < 0.001$). The reduction in LDL-C with anti-PCSK9 therapy compared with placebo was significantly greater than that compared with ezetimibe and placebo (placebo: 3.33% [CI, -6.83% to -0.16%]; $P < 0.001$; ezetimibe: -18.89% [CI, -23.29% to -14.49%]; $P < 0.001$). Sensitivity analyses stratified by type and dose of PCSK9 antibody showed consistent results [Table 2].

HDL cholesterol

11 RCTs comprising 5916 patients were included in the analysis of HDL cholesterol [Table 2 and Figure 2]. Overall, the percentage of increase with use of alirocumab versus no treatment with alirocumab was 6.15% (CI, (-0.75 to 13.05); $P < 0.01$). Change in HDL cholesterol levels were observed with placebo (-0.475% [CI, -3.975% to 3.025%]; $P < 0.001$) or ezetimibe 2.98% [CI, -2.72% to 8.68%]; $P < 0.001$). Findings of sensitivity analyses were consistent with the main results.

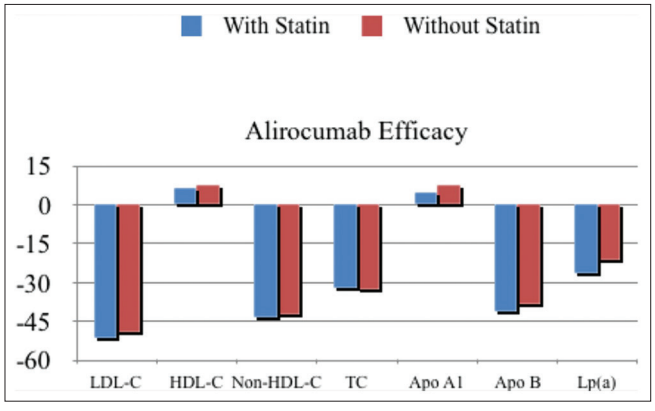

Figure 2: Sensitivity analyses for efficacy

APO B

11 RCTs including a total of 5916 patients were included in the analysis of Apo B. Overall, a greater than 40% reduction in Apo B levels was observed when alirocumab treatment was compared with no alirocumab treatment (MD, -42.09 [CI,-48.99 to -35.19%]; $P < 0.001$). A similar reduction in Apo B values was found in placebo-controlled trials (MD, -41.72% [CI, -44.57 to -37.97%]; $P < 0.001$) and in ezetimibe-controlled trials (MD, 37.82% [CI, -42.22 to -33.42%]; $P < 0.001$). Change in Apo B levels with placebo was 2 (CI -1.29 TO 5.3%) and with ezetimibe it was -12.12 (CI -16.52 to -7.71%). Sensitivity analyses for type and dose of alirocumab showed consistency in the direction and magnitude of the results [Table 2 and Figure 2].

Non HDL C

11 RCTs including a total of 5916 patients were included in the analysis of non HDL-C. Overall, greater than 40% reduction in non HDL-C levels was observed when anti-PCSK9 treatment was compared with no anti-PCSK9 treatment (MD, -42.36 [CI,-49.265 to -35.465%]; $P < 0.001$). A similar reduction in non HDL-C values was found in placebo-controlled trials (MD, -43.76% [CI, -47.26% to -40.26%]; $P < 0.001$) and in ezetimibe-controlled trials (MD, 40.11% [CI, --44.11 to -36.11%]; $P < 0.001$). Change in non HDL-C levels with placebo was 1.52 (-2.172 to 5.228%) and with ezetimibe it was -14.3 (CI -19.2% to 9.4%). Sensitivity analyses for type and dose of alirocumab showed consistency in the direction and magnitude of the results [Table 2 and Figure 2].

Lipoprotein (a)

11 RCTs including a total of 5916 patients were included in the analysis of lipoprotein (a). Overall, a greater than 23% reduction in lipoprotein (a) levels was observed when anti-PCSK9 treatment was compared with no anti-PCSK9 treatment (MD, -24.69 (-27.69% to -21.69%]; $P < 0.001$). A similar reduction in lipoprotein (a) values was found in placebo- controlled trials (MD, -24.02% [CI, -27.72% to -20.32%]; $P < 0.001$) and in ezetimibe-controlled trials (MD, 26.45% [CI, -30.45 to -22.45%]; $P < 0.001$). Reduction in lipoprotein (a) levels with placebo was -9.6 (-13.1 to 6.1) and with ezetimibe it was -4.54 (CI -8.9 to 0.09). Sensitivity analyses for type and dose of alirocumab showed consistency in the direction and magnitude of the results [Table 2 and Figure 2].

Total cholesterol (TC)

7 studies comprising 4771 patients contributed to the analysis of total cholesterol. Overall, a 32.65% reduction was observed when treatment with anti-PCSK9 treatment was compared with no anti-PCSK9 treatment (MD, 32.65% [CI, -39.55% to -25.75%]; $P < 0.001$). The reduction in total cholesterol with placebo (MD, - 0.65 (CI -7.55 to 6.25%]; $P < 0.001$) is less than with ezetimibe-12.75 (CI -19.65 to -5.85); $P < 0.001$). Sensitivity analyses by type and dose of anti-PCSK9 agent showed consistent results [Table 2 and Figure 2].

Table 1: Baseline characteristics of trials included in systematic review

Study	Patients, n	MeanAge, Y	Men%	CAD%	HT%	DM2%	BMI, kg/m^2	Mean LDLc level at baseline, mmol/L mean (mg/l)	Total cholesterol	HDL-C	Statin therapy, %	Intensive Statin therapy, %	Statin and Dose (mg)	Non-HDL-C	Apo B	Lp (a)	Fasting TG	ApoA1
ODYSSEY MONO	103	60.2	53.4	NA	NA	3.9	29.3	3.6 (139.7)	224 (0.8)	61 (0.5)	0	0	None					
ODYSSEY COMBO I	316	63	67.3	78.2	88.7	42.5	32.3	2.6 (102.1)	NA	48.3 (14.4)	99.7	62.7	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	130.0 (34.0)	90.8 (21.4)	31.0 (8.0:81.0)	130.0 (92.0:189.0)	
ODYSSEY COMBO II	720	61.5	73.6	90.1	81	30.9	30.2	2.8 (107.7)	4.8 mmols	1.2 mmols	99.9	66.7	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	3.6±1.0	0.9±0.2 g/L	1.0 (0.3, 2.5)	1.5 (1.1, 2.2)	
ODYSSEY LONG TERM	2341	60.5	62.3	68.6	NA	34.4	30.4	3.2 (122.4)	NA	49.8	99.9	44.1	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	152.6	101.9	21.5	133.5	147
ODYSSEY ALTERNATIVE	251	63.5	54.6	47	64.6	23.9	29	5.0 (192.3)	279.7	49.8	0	0	None	230	140	16	152	149.7
ODYSSEY OPTIONS I	112, 94	63.9, 64.1	57.1, 71.3	44.7, 72.3	79.5, 77.6	55.3, 43.6	31.9, 30.3	2.6 (102.2), 2.8 (107.7)	NA	48.7	100	0, 100	atorvastatin 20, atorvastatin 40					
ODYSSEY OPTIONS II	97, 107	61.3, 60.5	50.9, 55.2	NA	NA	NA	32, 30.2	2.7 (104.9, 3.1 (118.7)	NA	NA	100	0, 100	Rosuvastatin 10, Rosuvastatin 20,					
ODYSSEY FH I	486	52.1	55.7	45.5	43.0	9.9	29.0	3.7 (144.6)	NA	NA	100	82.7	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80					
ODYSSEY FH II	249	53.2	51.5	34.7	34.1	4.2	28.6	3.5 (134)	NA	NA	100	86.8	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80					
ODYSSEY CHOICE I	803	59.3	37.8	100		27	29.7	148.4 (36.8)	233.9 (41.9)	58.2 (15)	68	68	rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	-52.7 with 300 vs -0.3 (without statin) -58.8 vs -0.1 (with statin)				
ODYSSEY CHOICE II	233	63.1	53.4	46.6	63.8	15.5	28.5	158.5 (47.3)	244 (50.8)	10.5	0							
ODYSSEY HIGH FH	107	50.6	54.2	49.7	57.1	42.1	28.9	198.6	274.5	47.2			rosuvastatin 20-40, atorvastatin 40-80, or simvastatin 80	227.7	142.4	12.5	126.7	
	6019																	

Table 2: Percent change from baseline in calculated LDL-C at Week 24 (On-Treatment Analysis)

STUDY	LDL-C (95% CI) with Alirocumab	% reduction of LDL-C (95% CI) with placebo/Ezetimibe	HDL-C Alirocumab	placebo/Ezetimibe	Apo B Alirocumab	placebo/Ezetimibe	Non-HDL-C Alirocumab	placebo/Ezetimibe
ODYSSEY MONO (E)	-47.2	15.6	4.40					
ODYSSEY COMBO I	-48.2 (-52.5 to -39.3)	-0.2	3.5	-3.8	-36.7	-0.9	-39.1	-1.6
ODYSSEY COMBO II (E)	-52.4 (34.9 to 26.2)	-20.7	8.6	0.5	-40.7	-18.3	-42.1	-19.2
ODYSSEY LONG TERM	-61.0 (64.3 to 50.4)	0.8	4.0	-0.6	-52.8	1.2	-51.6	0.7
ODYSSEY ALTERNATIVE (E)	-45.0 (36.6 to 24.2)	-14.6	7.7	6.8	-36.3	-11.2	-40.2	-14.6
ODYSSEY OPTIONS I (E)	−48.4 (3.8), -50.5	-22.6 (3.9), -29.7 (3.2)	4.8, 7.7	−0.1 (2.1)	-33.7, −41.9	−10.1 (3.6)	-36.7, −47.6	−15.1 (4.0)
ODYSSEY OPTIONS II (E)	-51.55,	17.4 (4.2)	9.1, 7.2	4.0, -1.8	-36.5, -28.3	-9.7, -11.2	-42.7, -31.4	13.4, 12.9
ODYSSEY FH I	-48.8 (63.3 TO 52.6,	9.1	8.8,	0.8,	-41.1,	4.7	-42.8,	9.6,
ODYSSEY FH II	-48.7 (58.1 to 44.8)	2.8	6.0	0.8	-42.8	-3.5	-42.6	3.1
ODYSSEY (75 mg), CHOICE I (150 mg)	-50.9-55.75	-0.2	3.05, 3.05	-3.4	37.85, 42.65	1.9	-42.6, -26.5	0.3
ODYSSEY CHOICE II	-53.5, -51.7	4.7	7.4, 7.7	-2.4	-39.7, -38.9	7.5	-45.3, -44.2	4.8
ODYSSEY HIGH FH	-45.7 (51.1 to 27.1)	-6.6	7.5	3.9	-39.0	-8.7	-41.9	-6.2
MEAN	49.47	-0.525	6.21666666666667	0.225	-41.3833333333333	-1.125	-42.9166666666667	-1.92857142857143

STUDY	Lp (a) Alirocumab	placebo/Ezetimibe	TC Alirocumab	placebo/Ezetimibe	TG Alirocumab	placebo/Ezetimibe	ApoA1 Alirocumab	placebo/Ezetimibe
ODYSSEY MONO (E)								
ODYSSEY COMBO I	-20.55	-5.9	-27.9	-2.9	-6.0	-5.4		
ODYSSEY COMBO II (E)	-27.8	-6.1	-29.3	-14.6	-13.0	-12.8	-5.5	-1.3
ODYSSEY LONG TERM	-29.3	-3.7	-37.8	-0.3	-15.6	1.8	4.4	1.2
ODYSSEY ALTERNATIVE (E)	-25.9	-7.3	-31.8	-10.9	-9.3	—3.6	4.8	2.9
ODYSSEY OPTIONS I (E)	−23.6, -30.8	−10.6 (4.4)			-12, -19.1	−3.3 (4.1)		
ODYSSEY OPTIONS II (E)	-27.9, -22.7	4.3, 5.8			-11.2, -8.7	-8.3, -11.1		
ODYSSEY FH I	-25.2,	0.3,					-5.0	0.3
ODYSSEY FH II	-30.3	-1.6					-2.8	-1.6
ODYSSEY (75 mg), CHOICE I (150 mg)	-15.05, -20.3	8.05	-31.25-34.55	-1.35	-8.25, -14.3	-0.8	-4.8, -5.35	2.15
ODYSSEY CHOICE II	-21.8, -15.5	4.1	-34, -32.3	3.0	-10.6, -9.2	1.1	-8.2, -10.0	3.4
ODYSSEY HIGH FH	-23.5	-8.7	-33.2	-4.8	-10.5	-1.9		
MEAN	-26.225	-2.15	-32	-2.875	-10.88	-1.04	5.65	

Triglycerides

9 studies comprising 5181 patients contributed to the analysis of triglycerides. Overall, an 11.42% reduction was observed when treatment with PCSK9 antibodies was compared with no anti-PCSK9 treatment (MD, 11.42% [CI, -18.32 to -4.52%]; $P < 0.001$). A similar reduction in triglyceride values was found in placebo- controlled trials (MD, -10.63% [CI, -14.33% to -6.93%]; $P < 0.001$) and in ezetimibe-controlled trials (MD, 12.21% [CI, -16.21 to -8.21%]; $P < 0.001$). The reduction in triglycerides with placebo (MD, - - 0.98 (CI -5.38 to 3.42%]; $P < 0.001$) than with ezetimibe 0.8 (CI -6.1 to 7.7); $P < 0.001$). Sensitivity analyses by type and dose of anti-PCSK9 agent showed consistent results.

Apo A

7 studies comprising 4771 patients contributed to the analysis of Apo A. Overall, a 5.08% increment was observed when treatment with anti-PCSK9 treatment was compared with no anti-PCSK9 treatment (MD, 5.08% [CI, -11.98 to 1.82%]; $P < 0.001$). A similar Apo A value was found in placebo-controlled trials (MD, -5.79% [CI, -12.69% to 1.11%]; $P < 0.001$) and in ezetimibe-controlled trials (MD, 5.15% [CI, -12.05 to -1.75%]; $P < 0.001$) [Table 2 and Figure 2].

Discussion

The Phase 3 ODYSSEY program, consisted of 10 double-blind studies: five 12-18 months placebo-controlled studies (N = 3499) and five ezetimibe-controlled studies (N = 1797) that varied from 6-24 months in duration. All phase 3 studies either completed or surpassed a prespecified time point for treatment duration. A total of 5296 patients with hypercholesterolemia or mixed dyslipidemia were studied (including 3188 randomized to Alirocumab). 3 of the 10 studies were conducted exclusively in patients with heterozygous familial hypercholesterolemia (heFH) and one exclusively in patients with a documented history of statin intolerance. Except for the 103 patients in the MONO (monotherapy) study and 43 of 310 patients in the ALTERNATIVE (statin intolerance) study, all patients in the phase 3 program were at high or very high cardiovascular (CV) risk and all patients in the placebo-controlled studies were taking background lipid-modifying therapy (LMT) consisting of a maximally tolerated dose (MTD) of a high potency statin (atorvastatin, rosuvastatin, or simvastatin), with or without other LMTs. Of note, approximately 30% of all patients reported a history of diabetes mellitus. All patients were not at optimal LDL-C levels and required additional LDL-C reductions based on clinical treatment guidelines in effect at the time of study initiation. Eight studies (N = 2848 randomized), encompassing approximately half the patients in the phase 3 program, were designed such that patients started treatment with 75 mg every 2 weeks (Q2W) alirocumab and were up-titrated at week 12 in a blinded manner to 150 mg Q2W, if they had not reached their prespecified LDL-C goal at week 8. In the other two studies (N = 2448 randomized), encompassing approximately the other half of the patients in the phase 3 program, patients were treated with either placebo or alirocumab 150 mg Q2W for the entire study period. The primary efficacy endpoint in all studies was the percent reduction from baseline in LDL-C at week 24 compared to placebo.

Superior efficacy of alirocumab versus control was demonstrated in each of the ten phase 3 studies. At week 24, patients treated with alirocumab (on top of background therapy) achieved mean reductions in LDL-C which were significantly greater than those achieved with the addition of placebo or ezetimibe to background therapy. Averaged across the various studies, alirocumab use resulted in a mean -45.6 to -48.9% reduction in LDL-C from baseline to week 24 in studies that investigated the up-titration regimen and -60.4% in studies that solely investigated 150 mg Q2W dosing, whereas control rates were 0.5 to 4.2% (placebo) and -19.3 to -22.3%.

In a prespecified key secondary analysis, both alirocumab doses also demonstrated significantly greater LDL-C reductions than controls over the first 12 weeks of treatment, prior to potential up-titration: -44.5% on the 75 mg Q2W dose pooled across phase 3 placebo-controlled studies and -62.6% with the 150 mg Q2W dose. LDL-C reductions were sustained over the duration of treatment (up to 18 months) and were generally consistent across subgroups, regardless of type or dose of concomitantly used statin. In studies using the up-titration regimen, a majority of Alirocumab provides clinically meaningful mean reductions of LDL-C in patients not achieving adequate reductions with their existing statins or in patients unable or unwilling to take statins to achieve their LDL goals. In clinical studies, alirocumab had up to 63% mean reductions on top of statin therapy in patients with high cardiovascular risk who were not well controlled despite their current therapies, including those receiving a MTD of a highly-effective statin. This treatment effect is consistent with the >50% LDL-C reduction goal specified in the current guidelines for high-risk patient populations. In a randomized, double-blind study of patients with a history of statin intolerance, alirocumab demonstrated greater efficacy than ezetimibe and a lower rate of muscle-related adverse events than with either statin or ezetimibe treatment. These data indicate that alirocumab is a valuable treatment for patients who are unable or unwilling to take a statin and support the proposed indication in this patient population.

Significant difference in reduction of LDL-C was seen with alirocumab as compared to ezetimibe and placebo. Up to 40% of patients on statins are not able to attain their target LDL-C levels.[20] This can be attributed to sub-maximal dosing, pharmacological interactions of statins with other drugs, lack of adherence to treatment due to side effects, and inadequate LDL-C reduction despite doubling the dose.[17] Difference in reduction of LDL-C was seen in across all patient sub-populations. Significant difference in reduction of LDL-C was seen in both groups of patients with or without background statin therapy. This indicates towards the potential therapeutic application of alirocumab as an adjuvant to statin in case of inadequate control with alirocumab as well as substitute to statin in case of statin intolerance.

Treatment with statins is associated with rise in PCSK9 levels which attenuates the therapeutic effects of statins. Addition of

PCSK9 antibody alirocumab with statins can ameliorate this effect leading to additional reduction in LDL-C levels. As compared to stain monotherapy, addition of PCSK9 antibody to statins has resulted in additional 50-60% decrease in LDL-C levels.[12,21]

Reduction of LDL-C by 1% is associated with reduction in coronary events of a similar magnitude while reduction in LDL-C of ~40 mg/dL is associated with reduction in coronary events by ~22%.[22]

There was significant difference in increment of HDL-C was seen with alirocumab as compared to ezetimibe and placebo. This significant difference in rise of HDL-C was seen in both groups of patients with or without background statin therapy. Difference in increment of HDL-C was seen in across all patient subpopulations. In high-risk individuals, low HDL-C level with borderline LDL-C level is an indication for LDL-C lowering therapy. Among all the antidyslipidemic drugs, niacin is the most effective therapeutic agent to raise LDL-C levels. It is very important to consider treatment of dyslipidemia in candidate with low HDL-C even if they have LDL-C level in normal range.[23]

There was significant difference in reduction of Apo B was seen with alirocumab as compared to ezetimibe and placebo. This significant difference in reduction of Apo B was seen in both groups of patients with or without background statin therapy. Difference in reduction of Apo B was seen in across all patient subpopulations. Apo B levels are more accurate measure of the number of circulating LDL particles, thus, can be more reliable predictor of cardiovascular risk than LDL-C levels.[24]

There was significant difference in reduction of lipoprotein (a) was seen with alirocumab as compared to ezetimibe and placebo. This significant difference in reduction of lipoprotein (a) was seen in both groups of patients with or without background statin therapy. Difference in reduction of lipoprotein (a) was seen in across all patient subpopulations. Lipoprotein (a) plays contributory role in atherosclerotic plaque formation.[25] This reduction of lipoprotein (a) can have potential long term cardiovascular benefits. High lipoprotein (a) is associated with ASCVD evidences are lacking to associate lipoprotein (a) reduction decreases the risk.

There was significant difference in reduction of total cholesterol was seen with alirocumab as compared to ezetimibe and placebo. This significant difference in reduction of total cholesterol was seen in both groups of patients with or without background statin therapy. Difference in reduction of total cholesterol was seen in across all patient subpopulations.

There was significant difference in reduction of triglycerides was seen with alirocumab as compared to ezetimibe and placebo. This significant difference in reduction of triglycerides was seen in both groups of patients with or without background statin therapy. Difference in reduction of triglycerides was seen in across all patient subpopulations. Moderately elevated TGs are usually a component of metabolic syndrome with substantially higher risk for CVD.[26]

There was significant difference in increment of Apo A was seen with alirocumab as compared to ezetimibe and placebo. This significant difference in rise of Apo A was seen in both groups of patients with or without background statin therapy. Difference in increment of Apo A was seen in across all patient subpopulations. A low level of apoA1 is indicator of low serum levels of HDL-C and is a cardiovascular risk factor.[27]

In patients with hypercholesterolemia, alirocumab in combination with low- and high-dose atorvastatin decreased LDL-C to a greater extent than titration to high-dose atorvastatin, and considerably more patients who received the combination treatments reached LDL-C goals of <100 mg/dl or <70 mg/dl compared with patients who received atorvastatin treatment alone.[28]

In one recent meta-analysis, PCSK9 inhibitors were associated with small but significant increase in plasma glycemia and HbA_{1c}.[29] As per the American Diabetes Association (ADA) recommendations, addition of a PCSK9 inhibitor should be considered for patients with diabetes and ASCVD, if LDL cholesterol is ≥ 70 mg/dL on maximally tolerated statin dose.[30]

Although alirocumab lowers LDL-C as monotherapy, LDL-C lowering is greater in the presence of concomitant statin therapy. Statins inhibit HMG-CoA reductase and decrease cholesterol synthesis. This leads to an increase in cellular sterol regulatory element-binding-protein-2 (SREBP2) which up-regulates the transcription and ultimately, the surface expression of LDLR on hepatocytes.[31] The SREBP-mediated increase in surface LDLR is one of the main mechanisms of LDL-C lowering by statins. SREBP2, however, also promotes the transcription and expression of PCSK9, which dampens the ability of statins to clear circulating LDL particles. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the statin-induced increase in LDL-R density on hepatocytes, maximizing their potential lipid-lowering efficacy. Ezetimibe and fibrates have qualitatively similar but quantitatively smaller effects on PCSK9 levels. Thus this enhancement of the LDL-C lowering effect of alirocumab is also observed with ezetimibe and fibrates, but to a lesser degree. Lipid levels can be assessed as early as 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dosage adjusted accordingly.

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Conflicts of interest

There are no conflicts of interest.

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