PCSK9 Inhibitors: An Emerging Class of Medications

Journal of Pharmacy Technology
2016, Vol. 32(5) 201–209
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sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122516653970
pharmatech.sagepub.com

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Abstract

Objective: To evaluate the safety and efficacy of 2 human monoclonal antibodies, alirocumab and evolocumab, on reduction of low-density lipoprotein cholesterol (LDL-C), cardiovascular benefits, and their place in current practice. **Data Sources:** A search of MEDLINE and Scopus databases (1966 to May 2016) with search terms “alirocumab,” “evolocumab,” “LDL,” and “PCSK9.” **Study Selection and Data Extraction:** The search identified phase 3 randomized control trials in English language in the past 10 years that studied LDL-C reduction of alirocumab or evolocumab. The studies were assessed for all efficacy and safety endpoints. **Data Synthesis:** Twelve total studies were identified evaluating alirocumab or evolocumab. These monoclonal antibodies have been shown to significantly decrease LDL-C as monotherapy and in combination with statins in phase 3 clinical trials in patients with primary hypercholesterolemia as well as familial hypercholesterolemia by inhibiting PCSK9. Alirocumab significantly reduced LDL-C by up to 61%, while evolocumab significantly reduced LDL-C by up to 66%. Adverse effects of these medications have been low and overall well tolerated. **Conclusion:** Although these monoclonal antibodies have shown to significantly reduce LDL-C, their effect on cardiovascular outcomes has not yet been determined. Further studies are being conducted to assess the cardiovascular benefit of both alirocumab and evolocumab. Until these studies demonstrate a reduction in atherosclerotic cardiovascular disease risk, statins should remain first-line therapy for most patients. However, alirocumab and evolocumab can be used as an effective adjunctive therapy option to lower LDL-C or in patients who are statin intolerant.

Keywords

hyperlipidemia, coronary artery disease, cardiovascular drugs, lipids, drug trials

Introduction

The leading cause of death worldwide is coronary heart disease (CHD), with more than 7.4 million deaths annually.¹ Health care costs attributable to CHD in the United States are projected to triple to \$818 billion by 2030.² Hypercholesterolemia has been shown to be the primary risk factor for CHD, and using statins to reduce low-density lipoprotein cholesterol (LDL-C) improves mortality and lowers the risk of CHD events.³ Previous American and European guidelines used targeted LDL-C reduction as their primary goal to decrease cardiac events.^{4–6} Targets of <70 or <100 mg/dL, based on cardiovascular risk, were previously used; however, in 2013 the American College of Cardiology/American Heart Association (ACC/AHA) treatment guidelines changed practice and no longer endorse LDL-C goals. Instead, it identified 4 major statin benefit groups to reduce atherosclerotic cardiovascular disease (ASCVD) risk.⁷ This has led to an expansion of patients qualifying for statin therapy. European guidelines recommend at least a 50% reduction in LDL-C, while the ACC/AHA guidelines recommend high-intensity statins with LDL-C lowering ≥50% expected for most patients.⁷

For various reasons, patients may be unable to tolerate statin therapy or do not reach LDL-C reduction goals. Myalgias have been reported in up to 25% of current statin users and often lead to drug discontinuation or nonadherence.⁸ A meta-analysis of more than 200,000 patients on statin therapy demonstrated more than 6% of patients discontinued use.⁹ Achievement of LDL goals has been shown to be dependent on provider specialty, with 58% to 81% of high-risk patients using statin therapy unable to obtain the previous LDL-C goal of <70 mg/dL.^{10,11} Additional lipid lowering would be needed in these patients, and historically, other agents demonstrate only modest benefits. Increasing statin doses or changing to higher potency statins may only reduce LDL-C by 6% to 8%, whereas additional nonstatin lipid-lowering therapy may lower LDL-C by 10% to

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Table 1. Comparison Between Alirocumab and Evolocumab.

	Alirocumab ^{22,23}	Evolocumab ²⁴
Dosing (subcutaneously)	75 mg once every 2 weeks, may titrate to 150 mg once every 2 weeks after 4 to 8 weeks	140 mg once every 2 weeks or 420 mg once monthly
Time to peak	3-7 days	3-4 days
Volume of distribution	0.04 to 0.05 L/kg	3.3 L
Bioavailability	~85%	72%
Half-life at steady-state	17-20 days (12 days when administer with statin)	11-17 days
Adverse drug reactions (>5%)	Nasopharyngitis: 11% Injection site reactions: 7% Influenza: 5%	Nasopharyngitis: 6% to 11% Influenza: 8% to 9% Upper respiratory tract infection: 9% Injection site reactions: 6% Back pain: 6%

20%.^{7,12,13} Moreover, adding niacin has not shown to further reduce ASCVD risk in individuals treated to LDL-C levels of 40 to 80 mg/dL, and other nonstatin lipid-lowering agents have shown no reduction in ASCVD risk.^{7,14} Similarly, the ACCORD Lipid Trial found the combination of fenofibrate and simvastatin did not reduce ASCVD risk to a greater extent than adding placebo to simvastatin.¹⁵ There is need for an agent to reduce LDL-C and ASCVD risk when statin therapy alone is not sufficient or possible.

History

Low-density lipoprotein receptors (LDLR) are endocytic receptors that internalize lipoproteins and lipid-carrier complexes.¹⁶ Bound lipoproteins are released in the cell's endosome after endocytosis, which allows the LDLR to recycle to the cell surface. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds at the LDLR epidermal growth factor-like repeat A domain and inhibits the ability of LDLR to recycle back to the cell surface.¹⁷ Binding of PCSK9 to LDLR results in increased degradation of LDLR in the lysosome, which decreases the number of LDLR on the cell surface, increasing LDL-C levels.^{18,19} Inhibitors of PCSK9, therefore, allow increased recycling of LDLR, which decreases levels of LDL-C.^{18,19} A defect in the PCSK9 gene, which caused autosomal dominant hypercholesterolemia, led to the idea that this gene could be a target for LDL-C reduction. Research led to discoveries that mutations, causing a gain-of-function of PCSK9, resulted in hypercholesterolemia.^{20,21} A small subset

of black patients was found to have a loss-of-function mutation resulting in lower LDL-C and, surprisingly, a reduction in cardiovascular disease (CVD) risk. This was attributed to a 40 mg/dL reduction in LDL-C. These findings and investigations led to the development of monoclonal antibodies against PCSK9. Two antibodies, alirocumab and evolocumab, have recently been approved for the treatment of hyperlipidemia by the US Food and Drug Administration. The current labeled indication for these drugs is adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical ASCVD, who require additional lowering of LDL-C. Because the labeling states that it is adjunct to maximally tolerated statin therapy, this means that patients may be on no, low-, moderate-, or high-intensity statin. Additionally, evolocumab is also indicated for patients with homozygous familial hypercholesterolemia, adjunct to diet and other LDL-lowering therapies, who require additional lowering of LDL-C. Pfizer is currently investigating a third monoclonal antibody, bococizumab; currently only phase 1 and 2 trials have been published. This review analyzes the key phase 3 trials that have led to Food and Drug Administration approval of alirocumab and evolocumab and the impact they will have on future medicine. The dosing, pharmacokinetics, and adverse drug reactions are summarized in Table 1.²²⁻²⁴

Literature Review

A search of the literature was performed using MEDLINE and Scopus databases (1966 to May 2016) with search terms "alirocumab," "evolocumab," "LDL," and "PCSK9." The databases were searched using narrowing criteria of English language, publication in the last 10 years, and phase 3 randomized control trials. Studies looking at homozygous familial hypercholesterolemia were excluded. Twelve studies were included in our analysis.

Alirocumab

ODYSSEY MONO was the first study from the ODYSSEY program series and assessed efficacy and safety of alirocumab monotherapy versus ezetimibe.^{25,26} It was a double-blinded, active-controlled, double-dummy study (n = 103) evaluating the percent change in LDL-C from baseline to week 24. Patients were 18 years or older, with a 10-year risk of fatal cardiovascular (CV) events of 1% and 5% based on the European Systematic Coronary Risk Estimator (moderate risk), and a LDL-C between 100 and 190 mg/dL. Prior to screening, patients were not on any lipid-lowering agents, including statins, for 4 weeks (fibrates for 6 weeks). Patients had a mean age of 60 years, and 53% were male. Randomization, in a 1:1 ratio, occurred to either alirocumab 75 mg every 2 weeks plus an oral placebo daily or oral ezetimibe 10 mg daily plus a placebo injection every 2 weeks. It

was unknown if these patients were naïve to statin therapy. Up-titration to 150 mg of alirocumab occurred after week 8 if LDL-C was >70 mg/dL. Baseline LDL-C was 141 and 138 mg/dL for the alirocumab and ezetimibe groups, respectively. Secondary endpoints included percent change to week 12, other lipid parameters (Table 2), and a safety analysis. Results showed a significant reduction in LDL-C at week 24; 47% reduction in LDL-C for alirocumab versus 16% for ezetimibe ($P < .0001$). Favorable changes were seen in other lipid parameters when comparing alirocumab versus ezetimibe (Table 2). With this trial, alirocumab was shown to be safe and effective as monotherapy for a large portion of patients with hypercholesterolemia at moderate risk not receiving statin therapy.

ODYSSEY COMBO I was a 52-week double-blinded, placebo-controlled trial evaluating efficacy and safety of alirocumab in patients ($n = 316$) on stable, maximum tolerated statin therapy.²⁷ Patients ages 18 years or older with either LDL-C >70 mg/dL with established CVD, or LDL-C >100 mg/dL with CHD risk equivalents, were included. Maximum tolerated statin therapy was defined as atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg. Patients were randomized 2:1 to receive alirocumab 75 mg every 2 weeks or placebo, with dose escalation to 150 mg at week 8 if LDL-C was >70 mg/dL. The main efficacy outcome was the percent reduction in LDL-C at week 24 from baseline, with secondary outcomes listed in Table 2. The average age of study participants was 63 years, with over 62% males. The LDL-C reduction at week 24 from baseline was 48.2% alirocumab versus 2.3% placebo ($P < .0001$). At week 24, more than 75% of alirocumab patients and only 9% of placebo patients achieved an LDL-C of <70 mg/dL ($P < .00001$). Changes in the other lipid parameters and safety analysis were consistent with MONO (Table 2). This study improved on MONO by adding the standard of care statin to the medication regimen; however, it was only 52 weeks.

ODYSSEY COMBO II is an ongoing study being conducted with 720 patients. It is a 104-week study evaluating efficacy and safety of alirocumab compared to ezetimibe in patients on maximum tolerated statin therapy.²⁸ Results of the study are available from week 52, which is a prespecified analysis point. Inclusion criteria for this study were the same as in COMBO I, patients had hypercholesterolemia and were on maximum tolerated statin therapy. Allocation occurred in a 2:1 ratio to either alirocumab 75 mg every 2 weeks or ezetimibe 10 mg daily with matching placebos. Again, the dose was escalated to 150 mg alirocumab if LDL-C >70 mg/dL at week 8. Baseline characteristics were similar between groups. The average age was 61.6 years, and 73.6% of patients were men. Baseline LDL-C was 108 mg/dL for participants overall. The main efficacy endpoint, percent reduction in LDL-C at week 24 from baseline, was 50.6% and 20.7% ($P < .0001$) for alirocumab and ezetimibe

groups, respectively. Secondary outcomes can be seen in Table 2. Efficacy of alirocumab was shown across multiple subgroups, with results not differing based on demographics, region, medical history, diabetes, or intensity of statin therapy. Safety analysis showed similar rates of overall and serious adverse effects. The primary endpoint at week 24 was similar to previous studies; however, this study will continue to 104 weeks to maximize available efficacy and safety data.

ODYSSEY OPTIONS I was a double-blinded, double-dummy, parallel-group trial.²⁹ This trial aimed to compare addition of alirocumab versus other common lipid-lowering strategies. Patients at high or very high risk of CVD on stable doses of atorvastatin 20 or 40 mg with hypercholesterolemia were included. Patients were randomized into 1 of 4 groups: add-on alirocumab 75 mg every 2 weeks (Group 1); add-on ezetimibe 10 mg daily (Group 2); a doubling of their atorvastatin dose to 20 or 40 mg (Group 3); and if taking atorvastatin 40 mg, switching to rosuvastatin 40 mg (Group 4). A dose escalation of alirocumab to 150 mg was performed if LDL-C goal was not achieved by week 8. The primary endpoint evaluated the percent reduction in LDL-C from baseline to week 24. Baseline LDL-C was 99.7 mg/dL in the ezetimibe arm (Group 2) and 109.5 mg/dL in the alirocumab arm (Group 1) with an average age of 64 years and no significant difference in baseline characteristics. For Group 1, alirocumab lowered LDL-C by 44.1% and 54% ($P < .001$) when added to atorvastatin 20 and 40 mg, respectively. When these results are compared to each group, alirocumab had a significantly greater reduction ($P < .001$), Group 2 had a 20.5% and 22.6% reduction, and Group 3 had only a 5% and 4.8% reduction when added to atorvastatin 20 and 40 mg, respectively. Group 4 had only a 21.4% additional reduction when switched from atorvastatin 40 mg ($P < .001$), which is statistically significant when compared to Group 1 or alirocumab arm. Adverse events were similar across groups ($P = .9796$). Other lipid parameter changes are shown in Table 2. This study showed the advantage of alirocumab in reducing LDL-C compared to other lipid-lowering therapy when statin monotherapy was insufficient.

The ODYSSEY LONG TERM is a 78-week placebo-controlled, parallel-group, double-blind trial that includes the largest population ($n = 2341$) of patients for alirocumab to date.³⁰ Inclusion criteria of the study included patients 18 years or older, with heterozygous familial hypercholesterolemia or established CHD or a CHD risk equivalent, all with an LDL >70 mg/dL and receiving high-dose statin therapy or statin therapy at maximum tolerated dose for at least 4 weeks before screening. Allocation occurred to either alirocumab 150 mg or placebo every 2 weeks for 78 weeks in a 2:1 ratio. Baseline characteristics were similar, with a mean age of 60 years and baseline LDL-C of 122 mg/dL. Primary efficacy endpoint, similar to previous trials, was

Table 2. Results of Trials Evaluating Alirocumab and Evolocumab^a.

Study	Treatment	Baseline LDL-C (mg/dL)	LDL-C	HDL-C	TC	Non-HDL-C	TG	Apo A-I	Lp(a)	Apo B	LDL-C <70 mg/dL (%)
ODYSSEY COMBO I	Alirocumab	100.2	-48.2	3.5	-27.9	-39.1	-6.0	N/A	-20.5	-36.7	75
	Placebo	106	-2.3*	-3.8*	-2.9*	-1.6*	-5.4	N/A	-5.9*	-0.9*	9*
ODYSSEY COMBO II	Alirocumab	109	-50.6	8.6	-29.3	-42.1	-13	5.0	-27.8	-40.7	77
	Ezetimibe	105	-20.7*	0.5*	-14.6*	-19.2*	-12.8	-1.3*	-6.1*	-18.3*	45.6*
ODYSSEY LONG TERM	Alirocumab	122.8	-61.0	4.0	-37.8	-51.6	-15.6	4.0	-29.3	-52.8	79.3
	Placebo	122.0	0.8*	-0.6*	-0.3*	0.7*	1.8*	1.2*	-3.7*	1.2*	8*
ODYSSEY MONO	Alirocumab	141.1	-47.2	6	-29.6	-40.6	-11.9	4.7	-16.7	-36.7	N/A
	Ezetimibe	138.3	-15.6*	1.6	-10.9*	-15.1*	-10.8	-0.6*	-12.3	-11.0*	N/A
ODYSSEY OPTIONS I	Alirocumab ^b	109.5	-54.0	7.7	N/A	-47.6	-19.1	N/A	-30.8	-41.9	77.2
	Ezetimibe ^b	99.7	-22.6*	2.9	N/A	-21.0*	-13.9	N/A	0.2*	-14.3*	54.2*
RUTHERFORD-2 ^c	Evolocumab ^c	162.4	-61.3	8.1	N/A	-56.2	-16.1	7.3	-22.9	-49.8	N/A
	Placebo ^c	150.8	-2.0	-1.2	N/A	-1.4	3.5	-1.4	8.7	-0.7	N/A
LAPLACE-2 ^c	Atorvastatin 80 mg										
	• Placebo	100.3	14.5	5.0	9.34	11.8	6.7	N/A	-2.2	11.64	13.0
	• Ezetimibe	98.7	-14.6	0.6	-10.0	-14.3	-7.4	N/A	8.0	12.31	52.0
	• Evolocumab	94.2	-61.8	9.1	-36.3	-54.8	-10.1	N/A	-24.6	49.77	93.1
MENDEL-2 ^c	Evolocumab	142	-57.0	4.8	N/A	-50.1	-8.1	N/A	-20.4	-47.2	72.9
	Ezetimibe	143	-17.8	-2.8	N/A	-14.9	0.0	N/A	0.0	-13.2	1.4
	Placebo	140	0.1	-1.2	N/A	-0.3	-1.9	N/A	0.0	0.6	1.4
GAUSS-2 ^c	Evolocumab	192	-56.1	5.3	N/A	N/A	N/A	5.2	-27.0	-45.8	50.0
	Ezetimibe	195	-18.1	1.8	N/A	N/A	N/A	1.1	-1.7	-13.0	2.0
GAUSS-3	Evolocumab	218.8	-52.8	7.4	-36.6	-45.7	-2.9	N/A	-21.1	-43.5	27.4
	Ezetimibe	221.9	-16.7*	2.9*	-11.6*	-14.6*	-1.1	N/A	0.2*	-11.7*	0*
DESCARTES ^d	Evolocumab	100.4	-50.6	5.8	-28.2	-41.8	-2.6	2.2	-27.7	-41.3	82.3
	Placebo	100.2	8.7	0.4	5.3	8.4	9.0	-0.8	-5.4	2.9	6.4

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; Apo A-I, apolipoprotein A-I; Lp(a), lipoprotein a; Apo B, apolipoprotein B.

^aValues for evolocumab studies are those from biweekly dosing regimens.

^bTreatment with entry atorvastatin 40 mg arm.

^cResults are % change from baseline to 12 weeks.

^dResults are % change from baseline to 52 weeks.

*P < .05, results are % change from baseline to 24 weeks unless otherwise noted.

percent change in calculated LDL-C from baseline to week 24. The secondary outcomes of the study are listed in Table 2. The authors also performed a post hoc analysis on the composite end point of death from CHD, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. Results of the study showed similar reduction in LDL-C as the previous ODYSSEY trials. Mean percent change in calculated LDL-C from baseline to week 24 was -61.0% versus 0.8% comparing alirocumab to placebo ($P < .001$). Percent change in LDL-C from baseline to week 78 was -52.4% alirocumab versus 3.6% placebo ($P < .001$), illustrating persistent LDL-C reduction past previous trial endpoints. Changes in other lipid parameters are listed in Table 2. Myalgia was the only significant adverse event when comparing alirocumab to placebo (5.4% vs 2.9% ; $P = .006$). The post hoc analysis found that cardiovascular events occurred in 1.7% of alirocumab patients and 3.3% of placebo; hazard ratio 0.52 , 95% confidence interval 0.31 to 0.90 ($P = .02$). This study was able to confirm efficacy and safety in the largest population to date in a long-term study of 78 weeks compared to previous 24- and 52-week trials.

Evolocumab

MENDEL-2 is a multicenter, randomized, controlled study comparing 2 doses of evolocumab with ezetimibe and placebo in patients with primary hypercholesterolemia with no statin use or history of intolerance.³¹ Patients ($n = 615$) were randomized in a $1:1:1:1:2:2$ fashion to oral placebo and subcutaneous placebo every 2 weeks; oral placebo and subcutaneous placebo every 4 weeks; ezetimibe and subcutaneous placebo every 2 weeks; ezetimibe and subcutaneous placebo every 4 weeks; oral placebo and evolocumab 140 mg every 2 weeks; or oral placebo and evolocumab 420 mg every 4 weeks for 12 weeks. Baseline characteristics were similar across the 6 groups with a mean age of 53 years and mean baseline LDL-C of 143 mg/dL. Additional outcomes are listed in Table 2. Evolocumab every 4 weeks resulted in a 56.1% decrease in LDL-C compared to a 1.3% decrease with placebo and 18.6% decrease with ezetimibe at week 12 ($P < .001$). All adverse events or events of interest occurred at similar rates between groups. When used without a statin in patients with hypercholesterolemia, evolocumab significantly reduces LDL-C when compared to ezetimibe and placebo.

GAUSS-2 was a randomized, double-blind, placebo- and ezetimibe-controlled study that evaluated the safety and efficacy of evolocumab compared with ezetimibe in patients with hypercholesterolemia who were unable to tolerate at least 2 statins.³² A total of 307 patients 18 to 80 years of age on no or low-dose statin with LDL-C above their National Cholesterol Education Program Adult Treatment Panel III goal were randomized. Patients included had previously

experienced intolerance to at least 2 statins, defined as being unable to tolerate any dose or being unable to increase the dose above the smallest tablet strength due to muscle-related side effects. Mean age was 62 years with an average baseline LDL-C of 193 mg/dL. Patients were randomized $2:2:1:1$ to receive evolocumab 140 mg every 2 weeks plus daily oral placebo, evolocumab 420 mg every 4 weeks plus daily oral placebo, subcutaneous placebo every 2 weeks plus daily ezetimibe, or subcutaneous placebo every 4 weeks plus daily ezetimibe. Co-primary outcomes were percent change in LDL-C at week 12 from baseline and at the average of weeks 10 and 12. Percent reductions of LDL-C at a mean of weeks 10 and 12 were 56.1% with 140 mg of evolocumab every 2 weeks and 55.3% with 420 mg of evolocumab every 4 weeks from baseline when compared to ezetimibe, which resulted in a 36.9% and 38.7% reduction from baseline, respectively ($P < .001$). Overall, the rate of adverse events was higher in patients receiving ezetimibe. Study drug discontinuation occurred in 8% of the evolocumab patients and 13% of the ezetimibe patients as a result of adverse events. In patients with intolerance to 2 or more statins, evolocumab significantly reduced LDL-C. This study did not evaluate patients currently receiving statin therapy.

GAUSS-3 was a 2-stage, double-blind, 48-week randomized control trial that evaluated the efficacy and tolerability of evolocumab compared to ezetimibe in patients with muscle-related statin intolerance.³³ Patients included in phase A ($n = 491$) were 18 to 80 years of age. Additionally, they had to not tolerate atorvastatin 10 mg and any other statin; or 3 or more statins, with one being at the lowest average starting dose. In phase A, patients with CHD were included with an LDL-C ≥ 100 mg/dL. Patients without CHD were included with an LDL-C ≥ 130 mg/dL with 2 or more risk factors, ≥ 160 mg/dL with 1 or more risk factors, or ≥ 190 mg/dL with no additional risk factors. Phase A consisted of a crossover design, where patients were exposed to 10 weeks of atorvastatin 20 mg daily or placebo ($1:1$), followed by a 2-week washout period, and exposed to the alternate therapy for 10 more weeks. Patients who experienced muscle-related side effects from atorvastatin but not placebo were eligible for phase B. A total of 218 patients qualified for phase B, patients were randomized $2:1$ to either subcutaneous evolocumab 420 mg monthly or oral ezetimibe 10 mg daily for 24 weeks during which a double-blind, double-dummy design was used. Co-primary endpoints included mean percent change from baseline LDL-C to the mean of LDL-C at weeks 22 and 24 and the percent change from baseline LDL-C at week 24. Co-secondary endpoints are reported in Table 2. The mean age was 60 years with an average baseline LDL-C of 212.3 mg/dL for patients entering phase A and 219.9 mg/dL for patients entering phase B. The difference in the mean percent change from baseline LDL-C to the mean of weeks 22 and 24 was

37.8% ($P < .001$) in favor of evolocumab. During phase B, 28.8% of patients receiving ezetimibe and 20.7% of patients receiving evolocumab experienced muscle-related adverse events (no P value reported), with only one patient discontinuing evolocumab due to muscle symptoms. This study was not able to compare evolocumab to an alternative approach for patients with muscle-related statin intolerance. Nasopharyngitis, injection site reactions, influenza, and other previously reported adverse effects of evolocumab occurred at higher rates in the evolocumab group compared to the ezetimibe group. In patients with muscle-related adverse effects from statin therapy, evolocumab significantly reduced LDL-C levels after 24 weeks when compared to ezetimibe. The safety and efficacy of evolocumab was shown in this niche population, where lipid-lowering options are limited.

LAPLACE-2 was a multicenter, randomized, double-blind, placebo- and ezetimibe-controlled, 12-week study that evaluated the efficacy and safety of evolocumab in combination with moderate- or high-intensity statin therapy.³⁴ Patients ($n = 1899$) were 18 to 80 years of age with an LDL-C of ≥ 150 mg/dL at screening with no statin, ≥ 100 mg/dL at screening with nonintensive statin, or ≥ 80 mg/dL at screening with intensive statin (defined as atorvastatin ≥ 40 mg, rosuvastatin ≥ 20 mg, and simvastatin 80 mg or simvastatin plus ezetimibe) and fasting triglyceride levels of ≤ 400 mg/dL. Patients were randomized to 1 of 5 open-label, oral treatments after discontinuing previous statin and ezetimibe use. Patients received either a moderate-intensity statin (atorvastatin 10 mg, rosuvastatin 5 mg, or simvastatin 40 mg) or a high-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg) for 4 weeks. After 4 weeks of lipid-stabilizing, patients were randomized to evolocumab 140 mg every 2 weeks, evolocumab 420 mg every 4 weeks, or placebo every 2 or 4 weeks. Patients receiving atorvastatin were additionally randomized to either ezetimibe or placebo daily. The average age was 60 years with a mean LDL-C of 109 mg/dL. Co-primary outcomes were percent change in LDL-C at week 12 from baseline and the average of weeks 10 and 12. Table 2 shows additional secondary outcomes. A reduction in LDL-C of 59% to 66% with every 2 weeks dosing and 62% to 65% with every 4 weeks dosing occurred at the mean of weeks 10 and 12 ($P < .05$). Adverse events were similar for groups. In combination with moderate- to high-intensity statins, evolocumab significantly reduced LDL-C for patients with primary hyperlipidemia or mixed dyslipidemias.

RUTHERFORD-2 was a multicenter, randomized, double-blind, placebo-controlled study that assessed safety and efficacy of subcutaneously administered evolocumab every 2 or 4 weeks in 331 patients with heterozygous familial hypercholesterolemia with elevated LDL-C concentrations despite being on lipid-lowering therapy.³⁵ Patients were included in the study if they were 18 to 80 years of age with

a clinical diagnosis of heterozygous familial hypercholesterolemia at screening and on a stable dose of a statin with or without additional lipid-lowering therapy for at least 4 weeks prior to screening. Patients were randomized in a 2:2:1:1 ratio to receive 140 mg of evolocumab every 2 weeks, 420 mg evolocumab every 4 weeks, placebo every 2 weeks, or placebo every 4 weeks for 12 weeks. The average age of patients was 51 years while the average baseline LDL-C was 154 mg/dL. Baseline characteristics were similar between the 4 groups. Co-primary outcomes were percent change in LDL-C at week 12 from baseline and at the mean of weeks 10 and 12. There was a reduction in LDL-C of 59.2% at week 12 ($P < .001$) and of 60.2% at the mean of weeks 10 and 12 ($P < .001$) in the evolocumab 140 mg group. Evolocumab 420 mg resulted in a 61.3% reduction of LDL-C at week 12 ($P < .001$) and a 65.6% reduction at the mean of weeks 10 and 12 ($P < .001$). Results for other secondary outcomes and lipoproteins were also reported (Table 2). Again, adverse effects were similar between groups. Results of this study show a similar reduction in LDL-C from evolocumab in patients with heterozygous familial hypercholesterolemia as patients with primary hypercholesterolemia.

DESCARTES investigators conducted a multicenter, double-blind, placebo-controlled trial that compared evolocumab with placebo in patients with hyperlipidemia for 52 weeks, including a lipid-lowering period of 4 to 12 weeks.³⁶ Patients ($n = 905$) aged 18 to 75 years with an LDL-C of ≥ 75 mg/dL and a fasting triglyceride level of ≤ 400 mg/dL were included. Patients were assigned to 1 of 4 lipid-lowering groups, all of which included dietary restrictions. The groups included diet alone, atorvastatin 10 mg daily, atorvastatin 80 mg daily, and atorvastatin 80 mg daily plus ezetimibe 10 mg daily. After 4 to 12 weeks of open-label, background therapy, patients were randomized in a 2:1 ratio to receive 420 mg of evolocumab or placebo every 4 weeks for 48 weeks. The mean baseline LDL-C in both groups was similar at 104 mg/dL. The primary outcome was percent change in LDL-C at week 52 from baseline. Key secondary outcomes are provided in Table 2. The mean reduction in LDL-C in the evolocumab group was 57.0% at week 52 when compared to the placebo group ($P < .001$). Rates of adverse events were similar between the evolocumab and placebo groups. At 52 weeks, reduction in LDL-C remained consistent with the reduction seen after 12 weeks in other studies.

OSLER-1 and OSLER-2 were 2 open-label, controlled trials that aimed to gather long-term data on evolocumab by enrolling patients who had completed 1 of 12 parent trials.³⁷ Patients enrolled in the 12 parent studies were eligible to enroll in one of the extension studies if they did not experience any adverse events that led to discontinuation of the study drug, did not have an unstable medical condition, and would not need unblinded lipid measurements or adjustments

of background lipid-regulating therapy during the first 12 weeks of the extension study. Patients were assigned to a group as soon as possible after completion of the parent study. Randomization occurred in a 2:1 ratio to receive evolocumab plus standard therapy or standard therapy alone. Standard therapy was based on local guidelines for treating LDL-C. In OSLER-1, patients in the evolocumab group received 420 mg every 4 weeks. In OSLER-2, patients could choose to receive either 420 mg of evolocumab every 4 weeks or 140 mg every 2 weeks. A total of 4465 patients were enrolled in the OSLER program ($n = 1324$ in OSLER-1 and $n = 3141$ in OSLER-2). Mean patient age was 58 years, while median baseline LDL-C, before randomization into a parent study, was 120 mg/dL. The primary outcome for both OSLER-1 and OSLER-2 was the incidence of adverse events. A secondary outcome for both studies was the percent change from baseline in LDL-C. Safety endpoints for both studies included adverse events that led to discontinuation of the study drug, serious adverse events, abnormal creatinine kinase levels and liver enzymes, and the development of neutralizing antibodies against evolocumab. A prespecified exploratory outcome was the incidence of adjudicated cardiovascular events (death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, and heart failure requiring hospitalization). Adverse events occurred at a rate of 69.2% in the evolocumab group and 64.8% in the standard therapy group. Muscle-related, arthralgia, and injection-site reactions were the most common adverse effects. Only 2.4% of adverse events led to discontinuation of evolocumab. Evolocumab reduced LDL-C by 61% when compared with the standard therapy group at week 12 and was sustained over 48 weeks ($P < .001$). The exploratory analysis found the rate of cardiovascular events at 1 year was less in evolocumab group at 0.95% compared to 2.18% in the standard therapy group; hazard ratio 0.47, 95% confidence interval 0.28 to 0.78 ($P = .003$). Both 52-week trials evaluating evolocumab showed similar reduction in LDL-C after 52 weeks. OSLER-1 and OSLER-2 showed a similar rate of adverse events with evolocumab as with placebo.

Discussion

These phase 3 trials show that alirocumab and evolocumab significantly reduce LDL-C in a wide variety of patients. Patients included in these trials ranged from moderate to very high risk for CHD. Elevated LDL-C is responsible for 60% of CHD and 40% of ischemic strokes, and a reduction in LDL-C has been directly related to a reduction in cardiovascular events.³⁸ Current American guidelines recommend using a high-intensity statin, which approximately reduces LDL-C at least 50% in high-risk patients to reduce the risk of clinical ASCVD.⁷ Statins have a wide variety of benefits in addition to their LDL-C lowering effects. It has been

noted that statins have anti-inflammatory and pleiotropic effects, which further reduces ASCVD risk.³⁹

It is currently under investigation whether PCSK9 inhibitors also have additional benefits besides LDL-C reduction. ODYSSEY COMBO II showed that alirocumab did not reduce C-reactive protein, a common marker of inflammation, whereas statins have been shown to have this anti-inflammatory effect.⁴⁰ In phase 3 trials, alirocumab and evolocumab showed a reduction in LDL-C similar to that of some of the high-potency statin therapy options, reducing LDL-C up to 57% as monotherapy.³¹ Although PCSK9 inhibitors have shown similar LDL-C lowering effects as statins, it is unknown if they reduce ASCVD risk or have similar pleiotropic effects. While the results from OSLER-1 and OSLER-2 and ODYSSEY LONG TERM are promising, the results are limited.^{30,37} In order to investigate this, there are currently 2 major ongoing studies to determine whether PCSK9 inhibitors lower ASCVD risk and improve cardiovascular outcomes, FOURIER and ODYSSEY OUTCOMES.^{41,42} FOURIER has completed enrollment with more than 27 500 patients. Although the completion date is set for 2018, Amgen has stated that preliminary results may be released as soon as the end of 2016. ODYSSEY OUTCOMES is currently recruiting, but is estimating a study population of more than 18 000 patients. The study is not set to complete until 2018.

There is a lack of significant CV outcomes and long-term safety data when using PCSK9 inhibitors. The use of these medications will be determined by the outcomes of these trials, until then their use will be limited to patients unable to achieve a 50% reduction in LDL-C with heterozygous familial hypercholesterolemia or clinical ASCVD. Based on the literature reviewed, patients who cannot reach these goals because of intolerance or a weak response to statins may benefit from these medications. The long-term effects of these agents are unknown beyond the time frame studied, at most 78 weeks. Subsequently, it is unknown if long-term development of antibodies will occur and affect LDL-C levels. Patients should have confirmed adherence to their statin therapy with proven adverse effects to multiple statins before moving on to these second-line options.

Health systems and clinics will have to respond to formulary requests for these 2 new agents. Use of these medications at an institutional level will fall behind statins as first-line therapy and may fall even lower than other lipid-lowering medications (ezetimibe $\pm$ bile acid sequestrants). When considering which agent to recommend, it will be important for practitioners to consider cost, toxicities, and long-term effects. While phase 3 trials have shown slightly higher percentages in LDL-C reduction with evolocumab, there seem to be more adverse reactions associated with evolocumab, specifically those involving the upper respiratory tract. The wholesale acquisition costs of these agents for 28 days are similar, \$1120 for alirocumab and \$1085 for

evolocumab.^{43,44} Both manufacturers offer options to make these agents more accessible. Health care organizations must consider institution-specific cost analyses when determining coverage and formulary use of these medications until further data are published.

Without the results of the long-term studies, use of PCSK9 inhibitors is limited to strictly LDL-C reduction, not reductions in morbidity or mortality. PCSK9 inhibitors may have additional benefits beyond those of statins. Reduction in lipoprotein (a), which has been shown to be a risk marker of atherosclerosis, occurred in phase 3 trials with alirocumab and evolocumab.⁴⁵ This effect has not been shown with the use of statins alone. Many of these phase 3 trials used the combination of statins and PCSK9 inhibitors and were shown to be effective and safe in reducing LDL-C. Statins provide proven ASCVD risk reduction and should remain first line, while further studies are being completed that will address the potential ASCVD reduction provided by PCSK9 inhibitors.

Conclusion

PCSK9 inhibitors have been shown to lower LDL-C in patients with elevated LDL-C, familial hypercholesterolemia, and in patients intolerant to statins. However, a proven reduction in ASCVD risk or mortality has not yet been demonstrated. These agents should be considered for patients who require additional LDL-C lowering with statins or who are unable to tolerate statins. Additional studies are currently being completed with patient-oriented outcomes and will provide additional information to better clarify the exact role in therapy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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