Drug Class Review

Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) Inhibitors

Final Original Report

Executive Summary

July 2015

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Kim Peterson, MS
Brittany Holzhammer, MPH
Marian McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

INTRODUCTION

HMG-CoA reductase inhibitors, or statins, have been the primary therapeutic intervention for hypercholesterolemia for decades. They have been successful in reducing the risk of major cardiovascular (CV) events and mortality in a wide range of at-risk individuals. However, statins (alone or in combination with other lipid-lowering therapies, such as ezetimibe) are not always adequate in reducing cholesterol levels in some patients, even at higher doses (e.g., patients with heterozygous hypercholesterolemia). Additionally, some patients cannot tolerate statins. Within the last decade, the relationship between proprotein convertase subtilisin/kexin type 9 (PCSK9) and cholesterol metabolism has been increasingly studied. PCSK9 signals the degradation of the low-density lipoprotein receptor, which causes levels plasma low-density lipoprotein cholesterol to increase. Monoclonal antibodies directed at inhibiting PCSK9 are undergoing development as novel therapies in response to the therapeutic gaps posed by current standard therapies to treat hypercholesterolemia.

Scope and Key Questions

Currently, there are three PCSK9 inhibitors in phase III testing (Table A), which are the focus of this review. These interventions have not yet been approved by the U.S. Food and Drug Administration. The purpose of this review is to compare the benefits and harms of these drugs, with or without other lipid lowering drugs, with emphasis on health outcomes and longer-term harms.

Table A. PCSK9 Inhibitors Included in this Report

Generic Name	Company Code	Phase of Development	BLA Submitted	Estimated FDA Approval
Evolocumab	AMG 145	Phase II/III	8/28/14	Summer 2015
Alirocumab	SAR236553 (REGN727)	Phase III	11/27/2014	7/24/2015
Bococizumab	RN316 (PF-04950615)	Phase III	Unclear	2016

Abbreviations: BLA, biologics license application; FDA, U.S. Food & Drug Administration

In consultation with Drug Effectiveness Review Project participating organizations, the Pacific Northwest Evidence-based Practice Center drafted Key Questions and inclusion criteria reflecting populations, drugs, and outcome measures of interest to clinicians and patients. The following Key Questions were approved to guide this review:

1. What are the comparative benefits and harms of PCSK9 inhibitors in patients with heterozygous and homozygous familial hypercholesterolemia?

2. What are the comparative benefits and harms of PCSK9 inhibitors in patients with hypercholesterolemia who are unable to use statins due to intolerance or any other reasons?

3. What are the comparative benefits and harms of PCSK9 inhibitors in patients with non-familial hypercholesterolemia who have not achieved LDL-C <100 mg/dL or <70 mg/dL with their current lipid lowering regimen (e.g., statin, with or without ezetimibe, etc.)?

4. Do the comparative benefits and harms of PCSK9 inhibitors differ when used in different patient subgroups based on demographics, socioeconomic status, other medications, or comorbidities?

METHODS

To identify relevant studies, we searched Ovid MEDLINE® (through February Week 1 2015), the Cochrane Database of Systematic Reviews® (2009 through 2015), the Cochrane Central Register of Controlled Trials® (2009 through January 2015), and Scopus (2010 through 2015) using names of included drugs as search terms. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched ClinicalTrials.gov for unpublished results and additional publications. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches.

We assessed risk of bias (quality rating) of trials based on predefined criteria developed by the United States Preventive Services Task Force (ratings: good-fair-poor) and the National Health Service Centre for Reviews and Dissemination. We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.

RESULTS

Of 205 citations identified from electronic databases, 1 pharmaceutical manufacturer dossier submission, ClinicalTrials.gov, suggestions in public comments on the draft report and hand searches, we included 17 trials. We identified no completed studies with health outcomes as *primary* outcomes for alirocumab, bococizumab or evolocumab, but we identified ongoing studies with such primary outcomes for evolocumab (FOURIER) and for bococizumab (SPIRE-1 and SPIRE-2) with estimated completion dates in 2018. There were no published trials of bococizumab, despite 5 completed trials identified in ClinicalTrials.gov, 4 with completion dates between October 2011 and October 2013. There were no completed or ongoing studies that directly compared different PCSK9 inhibitors. The evidence is summarized below first by drug and then by population/Key Question, and in the Summary Table (Table B).

Part I. Evidence for Evolocumab

Heterozygous Familial Hypercholesterolemia

Compared to placebo, there was high-strength evidence from 2, 12-week randomized controlled trials (RCTs) (fair- and good-quality, N=499) that evolocumab, dosed at 140 mg every 2 weeks to 420 mg every 4 weeks, achieved a greater low-density lipoprotein cholesterol (LDL-C) reduction in patients who were largely taking a high-intensity statin plus ezetimibe with a greater improvement in high-density lipoprotein cholesterol (HDL-C) and no differences in harms (moderate-strength evidence).

Homozygous Familial Hypercholesterolemia

Low-strength evidence based on 1 small, good-quality trial (N=50) suggested that evolocumab 420 mg every 4 weeks reduced LDL-C significantly more than placebo at 12 weeks in patients taking a maximum statin dose and ezetimibe. There was no difference in HDL-C change and there was no difference in the percentage of patients with serious adverse events, neurocognitive events, or those withdrawing due to treatment emergent adverse events. However, compared with placebo, patients treated with evolocumab experienced fewer overall treatment emergent adverse events and potential injection-site reactions but more reports of gastroenteritis.

Statin Intolerant Patients

In statin-intolerant patients, 2 fair-quality 12-week RCTs (GAUSS and GAUSS-2; N=434) provided low-strength evidence that evolocumab led to a greater reduction in LDL-C when dosed at 280 mg every 4 weeks to or 140 mg every 2 weeks, while having generally similar effects on HDL-C and harms. There was also low-strength evidence from the GAUSS study (N=62) that the combination of evolocumab 420 mg every 4 weeks plus ezetimibe 10 mg led to a greater percent LDL-C reduction than ezetimibe 10 mg alone, but insufficient evidence to draw conclusions on other outcomes.

Patients Not Achieving LDL-C <100 mg/dL or <70 mg/dL While on Treatment for Hypercholesterolemia

Evolocumab Compared with Ezetimibe (Both with Statin Therapy)

In a comparison of evolocumab and ezetimibe (both with statin therapy), the LAPLACE-2 study (N=329), provided low-strength evidence that when added to either atorvastatin 10 mg or 80 mg, compared to ezetimibe 10 mg, evolocumab 420 mg monthly resulted in higher rates of meeting an LDL-C target of <70 mg/dL at 12 weeks, with similar rates of patients with overall adverse events. This study provided insufficient evidence to draw conclusions about HDL-C or serious adverse events or withdrawal due to adverse events, due to the small magnitude of change or event rates.

Evolocumab Compared with Placebo in Patients with Varying CV Risk

In short-term comparisons of evolocumab and placebo, LAPLACE-TIMI 57 AND LAPLACE-2 (N=996 for placebo comparison) provided high-strength evidence that at 12 weeks in patients with varying risk levels and not meeting LDL-C targets, significantly more patients taking evolocumab 420 mg monthly than taking placebo (both with statin therapy) achieved an LDL-C of <70 mg/dL, and had greater percent reduction in LDL-C. There was also moderate-strength evidence of modest HDL-C increases with evolocumab 420 mg monthly, and moderate- to high-strength evidence of no differences in harms outcomes.

Based on 1 good quality trial longer-term (N=901; 52 weeks) there was moderate-strength evidence that evolocumab 420 mg given every 4 weeks also resulted in significantly more patients achieving a goal of LDL-C <70 mg/dL compared with placebo, low-strength evidence of a modest increase in HDL-C, and evidence of no difference in harms (moderate- and high-strength depending on outcome). Clinically important and statistically significant differences were seen in all CV risk subgroups.

Evolocumab Compared with Placebo in Patients with High CV Risk

In patients with high CV risk, a small 12 week (N=104 for placebo comparison) study provided low-strength evidence that evolocumab 420 mg monthly resulted in higher rates of meeting LDL-C target of both <100 mg/dL and <70 mg/dL when added to statins in Japanese patients, compared to placebo. There was greater mean change in LDL-C, but insufficient evidence to draw conclusions about other outcomes.

Mixed Populations: Heterozygous Familial, Statin-Intolerant, and Not At Target

There was moderate-strength evidence, based on a pooled analysis of 2 open-label extension studies (OSLER 1 and 2) of patients completing 1 of 12 previous trials (patients not at target, with heterozygous familial hypercholesterolemia, or statin intolerance; N=4,465), that evolocumab 420 mg monthly or 140 mg every 2 weeks (plus standard care – primarily statins) reduced LDL-C by 61% more than standard care alone at 12 weeks. This reduction was largely sustained at 48 weeks (58.4% more than usual care at week 48). These studies also provided low-strength evidence of a greater proportion of patients meeting an LDL-C goal of <100 mg/dL or <70 mg/dL and a greater increase in HDL-C at 12 weeks than with standard therapy alone.

CV events were reported as secondary or post-hoc outcomes but evidence is insufficient to draw conclusions. There was low-strength evidence that slightly more patients on evolocumab experienced any adverse event at 12 weeks compared with statins alone, without differences in serious adverse events, but insufficient evidence to draw conclusions about other adverse event outcomes.

Part II. Evidence for Alirocumab

Heterozygous Familial Hypercholesterolemia

Compared to placebo, there was low-strength evidence that alirocumab achieved a higher LDL-C reduction in patients taking a maximum statin dose plus ezetimibe based on 1 fair-quality trial (N=77), with similar effects on HDL-C, but insufficient evidence to draw conclusions about harms. Evidence on alirocumab compared with placebo in patients taking a low- to moderate-intensity statin was insufficient (1 fair-quality RCT, N=22).

Homozygous Familial Hypercholesterolemia

No evidence for alirocumab.

Statin Intolerant Patients

No evidence for alirocumab.

Patients Not Achieving LDL-C <100 mg/dL or <70 mg/dL While on Treatment for Hypercholesterolemia

Alirocumab versus Placebo in Average-Risk Patients

Low-strength evidence from 2 small (N=154) fair-quality RCTs indicated that in patients stabilized on statins who had not achieved an LDL-C of <100 mg/dL, alirocumab 150 mg subcutaneously every 2 weeks for 8 to 10 weeks resulted in significantly more patients achieving study goal (LDL-C <100 mg/dL) and greater percent reductions (49% to 67% more) than statins alone. Evidence on adverse events and in subgroups, compared with statins alone, was insufficient due to small sample sizes.

Alirocumab versus Ezetimibe in High-Risk Patients

Moderate-strength evidence based on a good-quality trial (ODYSSEY COMBO, N=720), that alirocumab, 75 to 150 mg given every 2 weeks, resulted in a higher proportion of patients with high CV risk reaching study goal of LDL-C <70 mg/dL at 24 weeks (RR, 1.70; 95% CI, 1.46 to 1.95) than ezetimibe 10 mg. Similarly, the difference in the percent change in LDL-C at 24 weeks was -29.8% (P<0.0001) and the difference in change in HDL-C was 8.1% (mean baseline LDL-C 106 mg/dL; P<0.0001).

Alirocumab versus Placebo in High-Risk Patients

Based on 2 trials (ODYSSEY COMBO I and ODYSSEY Long-Term; N =2656), there was high-strength evidence that alirocumab, 75 to 150 mg given every 2 weeks, resulted in a higher proportion of patients with high CV risk reaching study goal of LDL-C <70 mg/dL at 24 weeks than placebo (pooled RR, 9.65; 95% CI, 7.7 to 12.0). The difference in percent reduction in LDL-C (-45.9% to -61.9%, P<0.001; mean baseline LDL-C range 100 to 123 mg/dL) and HDL-C (7.3% to 7.6%, P<0.001) were also greater.

There was moderate- and low-strength evidence of no difference in CV events between alirocumab and ezetimibe at 52 weeks or between alirocumab and placebo at 52 to 78 weeks (all with concomitant stain therapy). Moderate- and low-strength evidence found no differences in harms between alirocumab and ezetimibe or placebo (based on 3 trials), except for slightly more frequent injection site reactions with alirocumab in 1 study.

Part III. Evidence for Bococizumab

No completed studies.

OVERALL SUMMARY

Evolocumab and alirocumab both had evidence of large LDL-C reductions, with few differences in adverse event outcomes compared with placebo or ezetimibe. The strongest evidence (high-strength) for evolocumab was in heterozygous familial hypercholesterolemia and those at average CV risk who had not achieved LDL-C of <100 mg/dL or <70 mg/dL with primarily statin-based treatment. For alirocumab, the strongest evidence (high-strength) was in patients at high CV risk who had not achieved LDL-C of <100 mg/dL or <70 mg/dL with primarily statin-based treatment. Important questions remain about the effects of PCSK9 inhibitors on health outcomes and effects with longer-term use.

Table B. Summary of the evidence by drug and population

Population Study N Patient N	Concomitant lipid therapy	PCSK9 inhibitor Dose	Baseline LDL-C (mg/dL)	Difference in LDL-C change Difference in % meeting goal	HDL-C	Cardiovascular events	Harms
Evolocumab							
Heterozygous Familial Hypercholesterolemia: 12 wks							
2 RCTs N=499	High-intensity statin + ezetimibe	140 mg every 2 wks to 420 mg every 4 wks	150 to 155	-44% to -61% vs. placebo ★★★★	6.8% (*P*<0.01) to 9.2% (95% CI, +4.7% to +13.7%) ★★★	NR	No differences ★★★
Homozygous Familial Hypercholesterolemia: 12 wks							
1 RCT N=50	High-intensity statin + ezetimibe	420 mg every 4 wks	348	-32.1% (95% CI, -45.1 to -19.2) vs. placebo ★★	Evolocumab reduced HDL-C by 0.1% vs. placebo (NS) ★★	NR	No differences or lower rates of most harms, except more gastroenteritis ★★
Unable to use statins: 12 wks							
2 RCTs N=496	N/A	140 mg every 2 wks or 280 mg, 350, or 420 mg given every 4 wks (vs. ezetimibe 10 mg)	192 to 195	-26% (95% CI, -34.1% to -17.9%) for 280 mg every 4 wks to -38% (95% CI, -43.7 to -32.4) for 140 mg every 2 wks (vs. ezetimibe) ★★	Differences favored evolocumab for all doses (3.6% to 8.5%) ★★	NR	No difference in overall AEs and SAEs. Significantly lower WAEs with evolocumab (3% vs. 12%). No neurocognitive events and too few injection site reactions to draw conclusions. ★★ to ★

Population Study N Patient N	Concomitant lipid therapy	PCSK9 inhibitor Dose	Baseline LDL-C (mg/dL)	Difference in LDL-C change Difference in % meeting goal	HDL-C	Cardiovascular events	Harms
	Ezetimibe 10 mg	420 mg every 4 wks	NR	-47% (95% CI, -53.7% to -40.8%) ★★	No conclusions ★	NR	No conclusions ★
Not achieved LDL-C <100 mg/dL or <70 mg/dL **: 12-52 wks**							
Patients with varying risk of CV events: 12-52 wks 2 RCTs N=1,375	Statin, range of doses according to risk level	420 mg every 4 wks (vs. placebo)	104	Vs. placebo 52 wks: -57% (+/- 2.1 sd) LDL goal <70: 82.3% vs. 6.4% (*P*<0.0001) ★★★ 12 wks: -53% to -70.5% vs. placebo LDL goal <70: 71.8% to 94.5% vs. 0-9.3% ★★★★	52 wks: 5.4% (*P*<0.001) 12 wks: 4.5% (95% CI, 0.4 to 8.7) to 9.1% (95% CI, 4.4 to 13.7) ★★ to ★★★	NR	52 wks: no differences (vs. placebo) ★★ to ★★★ 12 wks: more overall AEs (60% vs. 42%), no difference in withdrawals, serious harms, injection site reactions ★★★ to ★★★★
Patients with high risk of CV events: 12 wks 2 RCTs N=1,375	Statin, range of doses	420 mg every 4 wks (vs. placebo or ezetimibe)	139 vs. placebo; 126 to 129 or 92 to 94 vs. ezetimibe	Vs. placebo: -63.9% (*P*<0.001) LDL goal <100: 96% vs. 1% (*P*<0.001) LDL goal <70: 82% vs. 0% (*P*<0.001) ★★ Vs. ezetimibe: LDL goal <70: 86% to 95% vs. 6% to 62% ★★	No conclusions ★	NR	Vs. placebo: no conclusions ★ Vs. ezetimibe: similar rates of overall AEs, but no conclusions on other harms outcomes ★★ to ★
Mixed population with extended duration: 12-48 wks							
2 extension RCTs N=4,465	Usual care (primarily statins)	420 mg every 4 wks	NR	Vs. placebo: 12 wks: reduction of 61% (95% CI, 59 to 63, *P*<0.001) LDL goal <100: 90.2% vs. 26.0% LDL goal <70: 73.6% vs. 3.8% 48 wks: 58.4% (*P*<0.001) ★★★ and ★★	12 wks: 8.7% vs. 1.7% (*P*<0.001) ★★	48 wks: any CV event (adjudicated, but not a primary outcome): HR, 0.47 (95% CI, 0.28 to 0.78) with evolocumab ★	48 wks: Overall AEs: 69.2% vs. 64.8%. No difference in serious adverse events. ★★ No conclusions for other harms ★

Population Study N Patient N	Concomitant lipid therapy	PCSK9 inhibitor Dose	Baseline LDL-C (mg/dL)	Difference in LDL-C change Difference in % meeting goal	HDL-C	Cardiovascular events	Harms
Alirocumab							
Heterozygous Familial Hypercholesterolemia: 12 wks							
2 RCTs N=98	High-dose statin + ezetimibe	150 mg, 200 mg, or 300 mg every 4 wks or 150 mg every 2 wks (vs. placebo)	151.0 to 170.1	-8% to -57% ★★	NSD except for 150 mg every 2 wks: +12.34% vs. +2.20% (*P*=0.0496) ★★	NR	No conclusions ★
***Not achieved LDL-C <100 mg/dL or <70 mg/dL* : 10-78 weeks**							
Patients with average risk of CV events: 10 wks 2 RCTs N=124 at 150 mg dose	Statin, range of doses	75 to 150 mg every 2 wks (vs. ezetimibe or placebo)	122.6 to 123.9	-49% to -67% LDL <100: 100% vs. 16% to 52% (150 mg every 2 wks) vs. placebo ★★	6% to 9% over placebo ★★	NR	No conclusions ★
Patients with high risk of CV events: 24-78 wks Vs. ezetimibe 1 RCT N=720 Vs. placebo 2 RCTs N=2,656	Statin, range of doses	75 to 150 mg every 2 wks (vs. ezetimibe or placebo)	106 (vs. ezetimibe) 100 to 123 (vs. placebo):	24 wks: Vs. ezetimibe: -29.8% (*P*<0.0001) LDL goal <70: RR 1.70 (95% CI, 1.46 to 1.95) ★★★ Vs. placebo: -45.9% to -61.9% (*P*<0.001) LDL goal <70: RR 9.65 (95% CI, 7.7 to 12.0) ★★★★	24 wks: Vs. ezetimibe: 8.1% over ezetimibe (*P*<0.0001) ★★★ Vs. placebo: 7.3% to 7.6% over placebo (*P*<0.0001) ★★★★	52 wks: No difference in CV events between alirocumab and ezetimibe ★★ 52 and 78 wks: No differences between alirocumab and placebo ★★★	No differences in harms outcomes between alirocumab and ezetimibe or placebo, except for slightly more frequent injection site reactions with alirocumab in one study. ★★ and ★★★

Strength of evidence: ★★★★=High; ★★★=Moderate; ★★=Low; ★=Insufficient
Abbreviations: AEs, adverse events; CI, confidence interval CV, cardiovascular; NR, not reported; NSD, no significant difference; RCT, randomized controlled trial; SAEs, serious adverse events; sd, standard deviation; WAEs, withdrawal due to adverse events; wks, weeks