PCSK9 Inhibitors: A New Method to an Old Madness?

Erika Hellenbart, PharmD, BCPS

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I have no personal or financial conflict of interest to disclose

Pharmacist Objectives

- Describe the mechanism of PCSK9 inhibitors in lipid management
- Explain benefits and limitations of PCSK9 inhibitors, including clinical data and financial implications in the appropriate selection of patients for which these agents may be beneficial

Technician Objectives

- Describe the mechanism of PCSK9 inhibitors in lipid management
- Explain appropriate administration of PCSK9 inhibitors

Patient Case

- 47 yo AAM with HTN and MI at age 37 and PCI x2 in 8/2012 despite atorvastatin 80mg and PCI in 4/2015 despite rosuvastatin 40mg. Pt denies EtOH, tobacco, illicit drug use.
- Pt is taking atorvastatin 80mg, ASA 81mg, clopidogrel 75mg, lisinopril 20mg and metoprolol XL 50mg daily
- 4/2015: TC 247; TG 208; HDL 48; LDL 157
- What would you recommend at this time?
  - Continue atorvastatin 80mg, assess adherence and lifestyle
  - Change atorvastatin to rosuvastatin 40mg daily
  - Initiate ezetimibe 10mg daily
  - Initiate alirocumab 75mg subcutaneously every 2 weeks

Current Treatment Guidelines

- 2013 ACC/AHA Guidelines
  - Changed approach to treating hyperlipidemia
  - Focus on ASCVD risk reduction
    - ASCVD risk calculator
  - Population based
    - Identified four groups that would benefit the most from treatment
    - Emphasis on medications proven to lower ASCVD events
    - Extensive evidence that appropriate **intensity** of statin therapy should be used to reduce ASCVD risk
  - Many limitations
    - Little guidance in CKD or HF
    - Possible overestimation of risk
    - Calculator limited to:
      - Statin-naïve
      - African Americans, Caucasians, "Other"

Stone NJ, et al. *Circulation*. 2014; 129(25 Suppl 2): S1-45

Current Treatment Guidelines

- 2014 NLA Recommendations
  - Patient-centered management
    - Risk factor calculation similar to ATP III guidelines
  - Reiterate usefulness of treatment goals
    - LDL monitoring
      - Facilitate communication with patients regarding goals/objectives
  - Appropriate intensity statin preferred

Jacobson TA, et al. *J Clin Lipidol*. 2014; 8(5): 473-88

Need for Additional Options

- Heart disease is still a leading cause of mortality in US
  - 1 in every 4 deaths
- Registry data in US (2008-2012) showed 32.4% of statin-eligible patients were not receiving statin
- Meta-analysis reported > 40% of patients on high-intensity statin did not reach LDL < 70 mg/dL
- Statin intolerance reported in approximately 15% of patients

Maddox TM, et al. *J Am Coll Cardiol*. 2014; 64(21): 2183-92
Boekholdt SM, et al. *J Am Coll Cardiol*. 2014; 64(5): 485-94
Fitchett DH, et al. *Circulation*. 2015; 131: e389-e391

Familial Hypercholesterolemia

- Worldwide prevalence approximately 1 in 500
  - HoFH much more rare
- Prevalence of CVD in middle-aged FH patients is 22-39% in Western countries
- Significantly greater lifetime risk of CV disease
  - 24-fold increase in MI by age 40 years
- Risk factors for CVD are similar to those without FH
  - Ex. Smoking, DM, established CHD, family hx of premature CHD, HTN, metabolic syndrome
  - Effect of each risk is amplified in FH patients
- Risk stratification algorithms underestimate risk

Robinson JG, et al. *J Clin Lipidol*. 2011; 5: S18-S29

Familial Hypercholesterolemia

- Risk factors are aggressively treated
  - BP per HTN or DM guidelines
  - Smoking cessation
  - Weight control, diet, exercise
- Drug therapy recommended in children and adults with LDL $\geq$ 190 mg/dL or non-HDL $\geq$ 220 mg/dL
  - Statins are initial treatment for adults
    - Goal of 50% reduction or LDL < 100 mg/dL in high-risk patients
  - Ezetimibe, niacin, or bile-acid sequestrants for intensification
- LDL apheresis
  - Children with HoFH
  - Adults refractory or intolerant to drug therapy

Add-On Therapy

- Many options to decrease LDL
- Lack of evidence proving reduction in CV events
  - Niacin: AIM-HIGH
  - Fenofibrate: ACCORD-Lipid
- Ezetimibe:
  - ENHANCE (2008):
    - Ezetimibe 10mg + simvastatin vs. simvastatin alone
    - Did not slow progression of atherosclerosis
    - Prescribing rates decreased

Boden WE, et al. *N Engl J Med*. 2011; 365(24): 2255-67
Ginsberg HN, et al. *N Engl J Med*. 2010; 362(17): 1563-74
Kastelein JJ, et al. *N Engl J Med*. 2008; 358(14): 1431-43

IMPROVE – IT

- Ezetimibe 10mg + simvastatin 40mg vs. simvastatin alone
- Primary outcome: composite of death from CVD, major coronary event, or nonfatal stroke
  - In stable patients with previous ACS and LDL within guideline recommendations
- Results:
  - Reduction in primary outcome (34.7% vs. 32.7%)
    - HR 0.936; 95% CI 0.89-0.99; p = 0.016
  - Reduction in LDL from baseline of 93.8 mg/dL to:
    - 53.7 mg/dL vs. 69.5 mg/dL (p<0.0001)
- Limitations:
  - Only moderate-intensity statin

Cannon CP, et al. *N Engl J Med*. 2015; 372: 2387-97

PCSK9 Inhibitors

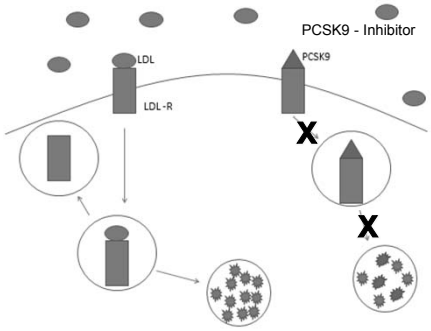
- Proprotein convertase subtilisin/kexin type 9
- PCSK9 Protein:
  - Binds to LDL-R → reduces LDL-R density on hepatocellular surface → increases circulating LDL
  - Gain of function mutation of PCSK9 gene found to be additional cause of familial hypercholesterolemia in 2003
  - Increased by inhibition of HMG-CoA reductase via increased expression of regulatory protein (SREBP-2)
  - Increased efficacy of statins through inhibition of PCSK9

Joseph L, et al. *Prog Cardiovasc Dis*. 2015; 58(1): 19-31

PCSK9 Inhibitors

- PCSK9 Inhibitors:
  - Human monoclonal antibody
  - Binds to PCSK9
    - Prevents PCSK9 from binding to LDL –R
    - Increases available hepatocyte LDL –R
    - Decreases circulating LDL

Regulation of LDL –Receptors



Available Products

	Alirocumab	Evolocumab
Trade name	Praluent	Repatha
FDA Approval	July 2015	August 2015
Approved Indication	Additional LDL lowering as adjunct to diet and maximally tolerated statin therapy in adults with: - Heterozygous familial hypercholesterolemia - Clinical atherosclerotic CV disease	Additional LDL lowering as adjunct to diet and maximally tolerated statin therapy in adults with: - Heterozygous familial hypercholesterolemia - Clinical atherosclerotic CV disease Adjunct to diet and other LDL-lowering therapy in adults with: - Homozygous familial hypercholesterolemia
Clinical Trial	ODYSSEY LONG TERM	OSLER
Dose	Self-administered injection 75mg subcutaneously every 2 weeks Max: 150mg every 2 weeks	Self-administered injection 140mg every 2 weeks 420mg once monthly HoFH: 420mg once monthly

Praluent (alirocumab) prescribing information
Repatha (evolocumab) prescribing information

Alirocumab Clinical Evidence

Study	Inclusion	Treatment	Efficacy	Safety
ODYSSEY LONG TERM Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events (4/2015)	N = 2341 (2:1 ratio) - Age ≥ 18 with HeFH, CHD, or CHD risk equivalent - LDL ≥ 70mg/dL on max tolerated statin	Alirocumab 150mg q2wks vs. placebo - 78 weeks - Mean study-drug exposure: 70 weeks - 47% on high-dose statin - 28% on other LLT (14% on ezetimibe) - 68-70% with CHD - 18% HeFH - Mean baseline LDL: 122 mg/dL	1^0: % LDL change at 24 wks: -61.0 vs +0.8% (p<0.001) ↓LDL to 48 vs 119 mg/dL LDL < 70 at 24 wks 79.3 vs 8% (p<0.001)	86 weeks Myalgias: 5.4 vs. 2.9% (p=0.006) Neurocognitive disorder: 1.2 vs. 0.5% Inj site rxns: 5.9 vs. 4.2% Ophtho: 2.9 vs. 1.9%

Post-hoc analysis of CV Events:
- Composite of death from CHD or unknown cause, nonfatal MI, fatal or nonfatal ischemic stroke, UA requiring hospitalization: 1.7 vs. 3.3% (HR 0.5; 95% CI 0.31-0.90; p=0.02)
- Non-significant when CHF and revascularization procedures were included.

Robinson JG, et al. *N Engl J Med*. 2015; 372(16): 1489-99

Evolocumab Clinical Evidence

Study	Inclusion	Treatment	Safety/Efficacy
OSLER Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events (4/2015)	N = 4465 (2:1 ratio) - Open label - Patients from phase 2 and 3 parent studies - LDL ≥ 70 to ≥ 100mg/dL on no to high-intensity statin Assigned on last day of parent trial if had not had adverse event leading to study drug d/c	OSLER 1 (N=1324): Evolocumab 420mg monthly + std tx vs. std tx alone for 56 weeks OSLER 2 (N=3141): Evolocumab 140mg q2wks or 420mg monthly for 48 weeks - Median f/u: 44 weeks - 70.3% on statin - 27% on high-intensity - 35% on mod-intensity - 13-15% on ezetimibe - 45% moderate to high risk per NCEP risk factors - 20% CAD - Median baseline LDL: 120-121 mg/dL	1^0: Incidence of adverse events: 69.2 vs. 64.8% Muscle-related: 6.4 vs. 6.0% Neurocognitive disorder: 0.9 vs. 0.3% Inj site rxns: 4.3% vs. N/A in std tx 2^0: % LDL change at 12 wks: -61.0% (p<0.001) ↓LDL by 73mg/dL to 48 mg/dL LDL < 70 at 12 wks 73.6 vs 3.8%

Post-hoc analysis of CV Events:
- Composite of death, MI, UA requiring hospitalization, coronary revascularization, stroke, TIA, and hospitalization for HF: 1.0% vs. 2.1% (HR 0.47; 95% CI 0.28-0.78; p=0.003)

Sabatine MS, et al. *N Engl J Med*. 2015; 372(16): 1500-9

Study Considerations

- Patient populations
  - Alirocumab trial included high-risk patients
    - FH, CHD, or CHD equivalent on high or max-tolerated statin
    - Greater clinical applicability
  - Evolocumab trial with lower risk patients
    - Fewer patients on statins
- Possible bias with evolocumab trial
  - Patients had to successfully complete parent trial by tolerating and being adherent to injections
  - Open-label trial

Study Considerations

- Relatively short follow-up time
- Higher incidence of neurocognitive events
  - Further exploration is necessary
- Both showed significant decrease in rate of composite CV outcomes
  - However, low overall incidence in both
- Similar rates of adverse effects with LDL < 25 mg/dL

Evolocumab & HoFH Indication

- TESLA-B Trial
  - Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities
- Patients ≥ 12 years with homozygous FH (HoFH)
  - On LLT for 4 wks; could not have received apheresis
  - 50 patients included
  - Mean age 31 years
    - 10 patients (7 in study group) were age 13-17 years
  - 90% Caucasian
  - Mean baseline LDL 349 mg/dL on atorvastatin or rosuvastatin
    - 92% on ezetimibe
- 31% reduction in LDL between evolocumab and placebo from baseline to week 12
  - 95% CI -44% to -18%; $p < 0.001$

Raal FJ, et al. *Lancet*. 2015; 385:341-50

Potential Place in Therapy for PCSK9 Inhibitors

- Current ACC/AHA guidelines do not recommend targeting specific LDL goals
- NLA guidelines recognize utility in LDL targets and potential for PCSK9 inhibitors
- FH and high-risk CVD patients
  - Uncontrolled or intolerant to high-intensity statin therapy
- Results of IMPROVE-IT favor trial of ezetemibe prior to PCSK9
  - Many insurances requiring this
- CV outcomes are promising but short follow-up and not included as primary endpoint
  - Further information is necessary

Ongoing Studies

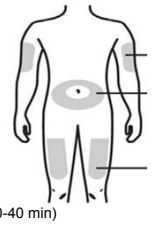
- ODYSSEY Outcomes
  - Currently recruiting; estimated completion by 2/2018
  - Objective: Effect of alirocumab vs. placebo on occurrence of CV events in patients with ACS 4-52 weeks prior
    - In addition to evidence-based medical and dietary management
    - Composite endpoint: death from CHD, non-fatal MI, fatal and non-fatal ischemic stroke, UA requiring hospitalization
    - 64 month treatment period and 2 month follow-up
- FOURIER
  - No longer recruiting; estimated completion by 2/2018
  - Objective: Effect of evolocumab vs. placebo on time to CV death, MI, or stroke
    - In addition to "effective statin therapy": ≥ atorvastatin 20mg or equivalent
    - Patients with clinical CVD disease at high risk for recurrent event

NLM Identifier: NCT01663402
NLM Identifier: NCT01764633

Cost & Access Considerations

- Annual cost:
  - Alirocumab - $14,600
  - Evolocumab - $14,100
- Express Scripts covers both
  - Restricted access
  - Cap per year
- Both manufacturers have copay cards
- Require prior authorization
  - Pharmacists vs. HUB
  - HUB:
    - Must disclose household income
    - Sign authorization allowing company to contact patient regarding marketing studies, promotions, etc.

Other Considerations



- Storage:
  - Must be stored in refrigerator
  - Room temperature:
    - Evolocumab – 30 days
    - Alirocumab – 24 hours
- Administration:
  - Allow injection to warm to room temp (at least 30-40 min)
  - Wash hands and use alcohol wipe to clean injection area
  - Medicine in window should be clear to slightly yellow
  - Injection sites: thigh, upper arm, stomach (>2" from belly button)
  - Pull off cap
  - Firmly push autoinjector on skin at 90^0
  - Push start button until hear click, continue holding pen against skin
  - Injection takes 15-20 sec
  - Remove pen once window turns yellow
  - Dispose in sharps container

Patient Case

- 47 yo AAM with HTN and MI at age 37 and PCI x2 in 8/2012 despite atorvastatin 80mg and PCI in 4/2015 despite rosuvastatin 40mg. Pt denies EtOH, tobacco, illicit drug use.
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Conclusion

- Utility in very high risk patients
  - On max tolerated statin and trial of ezetimibe
  - Other risk factors minimized (HTN, smoking, etc.)
- Pharmacy will play significant role
  - Prior authorization vs. HUB
  - Administration education
- Results of long-term CV and safety studies will dictate widespread acceptance

Self-Assessment

Which of the following describes the mechanism of action of PCSK9 inhibitors?

a. Directly binding to LDL for uptake and metabolism by liver
b. Increases available LDL receptors by binding to PCSK9
c. Promote degradation of LDL receptors
d. Directly binding to LDL receptors to facilitate binding of LDL

Self-Assessment

Which of the following is FALSE regarding administration of PCSK9 inhibitors?

a. Possible injection sites are upper arms, stomach, or thigh
b. Push injection to skin at 90^0 angle
c. Release pen from skin as soon as start button is pushed and “click” is heard
d. Medicine in window should be yellow when dose has been administered

Self-Assessment

In which of the following patients would you recommend a PCSK9 inhibitor?

a. A 61 yo male with CVA at age 57 and LDL of 120 mg/dL on atorvastatin 20mg daily
b. A 53 yo female with MI at age 40 and LDL of 168 mg/dL on rosuvastatin 40mg daily
c. A 46 yo male with HTN, DM, and hyperlipidemia with an A1c of 10.3% and LDL of 151 mg/dL on simvastatin 20mg daily
d. A 75 yo female with HTN and LDL of 113 mg/dL not currently on lipid-lowering therapy

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Abbreviations

- ACC/AHA: American College of Cardiology
- NLA: National Lipid Association
- ASCVD: Atherosclerotic cardiovascular disease
- ACS: Acute coronary syndrome
- UA: Unstable angina
- MI: myocardial infarction
- CVD: Cardiovascular disease
- CHD: Coronary heart disease
- HoFH: Homozygous familial hypercholesterolemia
- HeFH: Heterozygous familial hypercholesterolemia

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