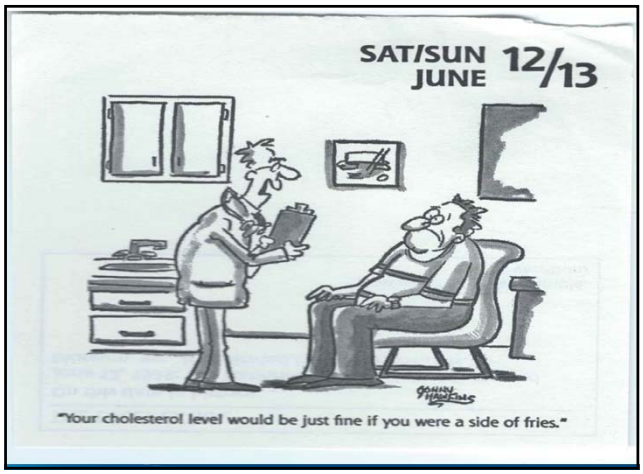
Injectable LDL Lowering Medicines

Katie Manou, PharmD
Seth M. Jacobson, MD

Medicine of the Highest Order



Objectives

- Describe place in therapy for PCSK9 inhibitors
- List steps for proper injection technique for Praluent (alirocumab) and Repatha (evolocumab)
- Identify cardiology office's role in PCSK9 inhibitor initiation

Medicine of the Highest Order

Patient Case

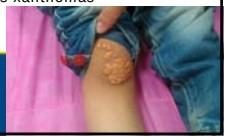
JL is a 47 year-old WM with Heterozygous Familial Hypercholesterolemia. His LDL off of treatment is 359 mg/dL and his father died of a heart attack at age 54. He has tried five different statins and ezetimibe, all of which caused him severe myalgia. He comes into the office today asking about the new biologic medications for hyperlipidemia he has been reading about.

Is he a candidate for a PCSK9 inhibitor?

Medicine of the Highest Order

Familial Hypercholesterolemia (FH)

- Heterozygous familial hypercholesterolemia (HeFH) is the most common autosomal dominant genetic disorder
  - 1:200 to 1:500
  - Have elevated LDL due to impaired functioning of LDL receptor
  - 100-fold risk of CV events if untreated
- Homozygous familial hypercholesterolemia (HoFH)
  - 1:1,000,000
  - Extremely elevated LDL due to significant LDL receptor dysfunction or absence
  - Typically diagnosed in childhood by cutaneous xanthomas

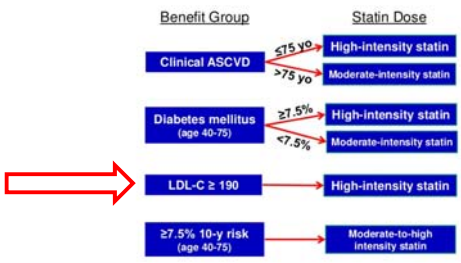


Kastelein JJP et al. *Eur Heart J.* 2015. doi: 10.1093/eurheart/ehv370
Gidding SS et al. *Circulation.* 2015. doi: 10.1161/CIR.0000000000000297.

Medicine of the Highest Order

Treatment of FH

- 4 statin benefit groups



Stone NJ, et al. *Circulation.* 2013.
Gidding SS et al. *Circulation.* 2015. doi: 10.1161/CIR.0000000000000297.

Medicine of the Highest Order

PCSK9 Inhibitors

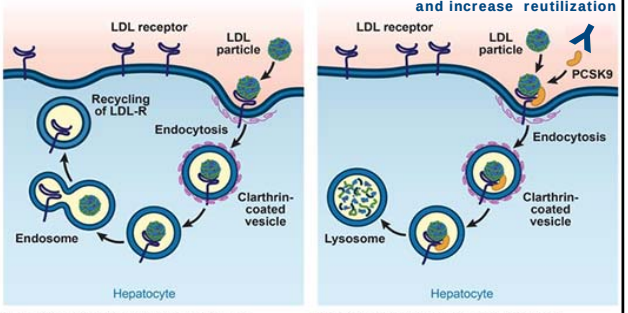
- PCSK9 inhibitors are monoclonal antibodies indicated as add-on therapy for patients with:
  - Familial Hypercholesterolemia
  - Clinical atherosclerotic cardiovascular disease (ASCVD)

Brand	Praluent	Repatha
Generic	Alirocumab	Evolocumab
Manufacturer	Sanofi and Regeneron Pharmaceuticals, Inc.	Amgen Inc.
FDA Approval	July 24th, 2015	August 27th, 2015

7

PCSK9 Mechanism of Action

PCSK9 inhibitors reduce LDL Receptor degradation and increase reutilization



LDL degradation and recycling of LDLR

PCSK9-mediated degradation of LDLR

Lambert G, et al. *J. Lipid Res.* 2012;53:2515-2524.[6]

Praluent® (alirocumab)

Indication: Adjunct to diet and maximally tolerated statin therapy in:
- HeFH
- ASCVD

Dosage: 75 mg SQ every 14 days (may be increased to 150 mg)

Dosage forms: 75 mg/mL or 150 mg/mL
- Auto-injector
- Pre-filled syringe

ADRs: Nasopharyngitis, injection site reactions, and influenza

9

Praluent (alirocumab) [Package Inset]. 2015. Sanofi-aventis and Regeneron, Inc.

Alirocumab clinical trials

Study	Patient Population (Maximally tolerated statin ± lipid-lowering therapy, LDL not at goal)	Intervention	Mean LDL Change from Baseline at Week 24
FH I & FH II (n=735)	HeFH (45% ASCVD) Mean baseline LDL: 141 mg/dL	• Alirocumab 75 mg every 14 days vs. placebo	-51% versus +3% with placebo (p<0.0001)
COMBO I (n=316)	Hyperlipidemia (84% ASCVD) Mean baseline LDL: 102 mg/dL	• Alirocumab 75 mg every 14 days vs. placebo	-48% versus -2% with placebo (p<0.0001)
ODYSSEY LONG TERM (n=2,341)	HeFH and/or ASCVD (69% ASCVD only and 18% HeFH only) Mean baseline LDL: 122 mg/dL	• Alirocumab 150 mg every 14 days vs. placebo	-62% versus +1% with placebo (p<0.0001)

10

ODYSSEY LONG TERM Post Hoc Analysis

Cardiovascular Event	Placebo (%)	Alirocumab (%)	P-value
Death from CHD, including unknown cause	0.9	0.3	0.26
Non-fatal MI	2.3	0.9	**0.01**
Fatal or nonfatal ischemic stroke	0.3	0.6	0.35
Unstable angina requiring hospitalization	0.1	0	0.34
Composite CV events	**3.3**	**1.7**	**0.02**

11

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

Repatha® (evolocumab)

Indication: Adjunct to diet and maximally tolerated statin therapy in:
- HeFH
- ASCVD
- HoFH

Dosage:
- **HeFH or ASCVD:** 140 mg SQ every 14 days or 420 mg SQ once monthly
- **HoFH:** 420 mg SQ once monthly

Dosage forms: 140 mg/mL SureClick Pens or pre-filled syringes

ADRs: Nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions

12

Repatha (evolocumab) [Package Inset]. 2015. Amgen Inc.

Evolocumab clinical trials

Study	Patient Population (Maximally tolerated statin ± lipid-lowering therapy, LDL not at goal)	Interventions	Mean LDL Change from Baseline at Week 12
LAPLACE-2 (n=2067)	Hyperlipidemia (30% ASCVD) Mean baseline LDL: 108 mg/dL	Evolocumab 140 mg every 2 weeks or 420 mg monthly vs. placebo	-64% versus -1% with placebo (p<0.0001) with background atorvastatin 80 mg
RUTHERFORD-2 (n=331)	HeFH (38% ASCVD) Mean baseline LDL: 156 mg/dL	Evolocumab 140 mg every 2 weeks or 420 mg monthly vs. placebo	-62% versus -1% with placebo (p<0.0001)
TESLA Part B (n=49)	HoFH (43% ASCVD) Mean baseline LDL: 162 mg/dL	Evolocumab 420 mg monthly	-23% versus +8% with placebo (P<0.0001)

13

Limitations of Alirocumab and Evolocumab

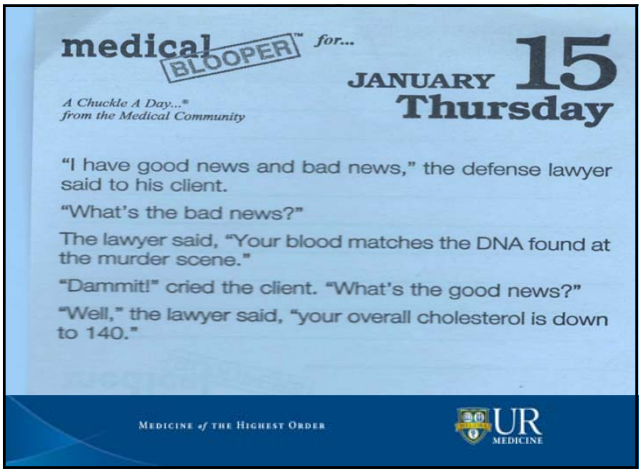
CV morbidity and mortality

- Currently, do not have prospective data
  - Being studied prospectively in ODYSSEY OUTCOMES and FOURIER

Statin intolerance

- Limited evidence
  - Being studied in ODYSSEY ALTERNATIVE and GAUSS-3

14



Patient Case

JL is a 47 year-old WM with Heterozygous Familial Hypercholesterolemia. His LDL off of treatment is 359 mg/dL and his father died of a heart attack at age 54. He has tried five different statins and ezetimibe, all of which caused him severe myalgia. He comes into the office today asking about the new biologic medications for hyperlipidemia he has been reading about.

Is he a candidate for a PCSK9 inhibitor?

16

Patient Case 2

- NS is a 74 year-old WM with CAD and history of NSTEMI.
- Current medications:
  - Atorvastatin 80 mg daily
  - Ezetimibe 10 mg daily
  - Lisinopril 40 mg daily
  - Metoprolol XL 100 mg daily
  - Aspirin 81 mg daily
- LDL 106 mg/dL

Is he a candidate for a PCSK9 inhibitor?

17

Patient Case 3

- NS is a 74 year-old WM with CAD and history of NSTEMI. He recently had to discontinue atorvastatin 80 mg daily due to myalgia.
- Current medications:
  - Ezetimibe 10 mg daily
  - Lisinopril 40 mg daily
  - Metoprolol XL 100 mg daily
  - Aspirin 81 mg daily
- LDL 106 mg/dL

Is he a candidate for a PCSK9 inhibitor?

18

Coverage tips

- LDL must be within 30 days of prescription for PCSK9 inhibitor
- Must be taking maximally tolerated statin + ezetimibe
  - If cannot tolerate need careful documentation
    - Dose
    - Timeframe
    - Reason for discontinuation and if symptoms resolved after
- Must document diet and exercise modifications
- HeFH must meet definition for definite diagnosis per Simon Broome or WHO criteria
- Easier to show clinical ASCVD in most patients
  - Can use imaging to show ASCVD in patients without history of CV event

19

Highlighted Differences

Praluent	Repatha
•Not indicated for HoFH	•Indicated for HoFH
•Stable at room temperature for 24 hours	•Stable at room temperature for 30 days
•Option of titrating dose up	•Latex cap and tip

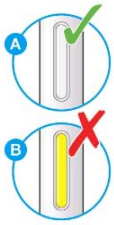
★ At this time considered clinically equivalent

20

Praluent (alirocumab) and Repatha (evolocumab) Pen Administration

1. Store in refrigerator
   a. Praluent maximum of 24 hours at room temp.
   b. Repatha maximum of 30 days at room temp.

2. Look at the window

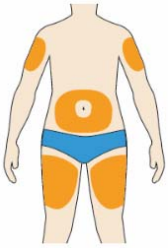


21

Praluent (alirocumab) and Repatha (evolocumab) Pen Administration

3. Warm to room temp.

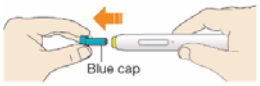
4. Prep injection site



22

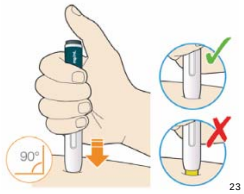
Praluent (alirocumab) and Repatha (evolocumab) Pen Administration

5. Pull off cap



orange cap for Repatha (evolocumab)

6. Press down at 90° angle
   a. Make sure yellow safety tip pressed in



23

Praluent (alirocumab) and Repatha (evolocumab) Pen Administration

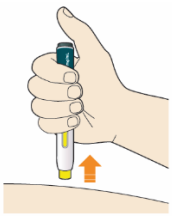
7. Push and immediately release grey button

8. Keep holding pen against skin until window completely yellow

24

Praluent (alirocumab) and Repatha (evolocumab) Pen Administration

9. Lift pen straight off skin

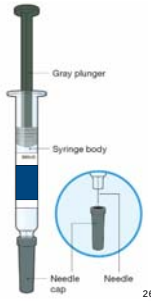


10. Discard in sharps container

25

Praluent (alirocumab) and Repatha (evolocumab) Syringes

- Syringes are a good option for patients who have:
  - Pain with pen injections
  - Experience with self-injections
  - No fear of seeing the needle



26

Praluent (alirocumab) and Repatha (evolocumab) Syringe Administration

1. Check to make sure solution is clear
2. Warm to room temperature
3. Prep same injection sites
4. Pull off needle cap
5. **Pinch skin and insert with dart-like motion**
6. Make sure syringe is empty them pull out from skin at same angle entered
7. Do not recap. Discard in sharps container.

27

Administration Troubleshooting

28

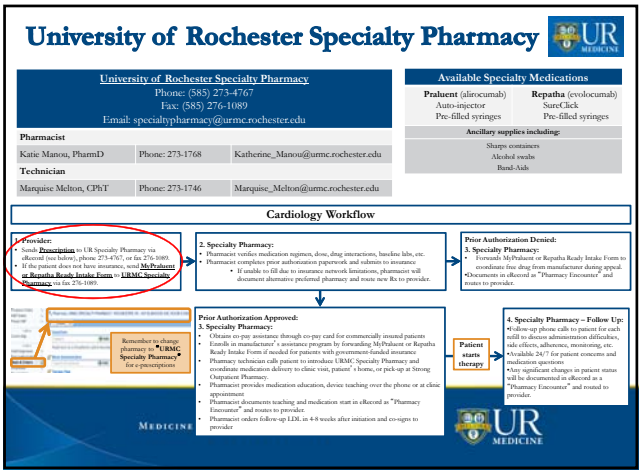
Cost Concerns

- Each approximately $1,400 per month

Insurance	Praluent (alirocumab)	Repatha (evolocumab)
Commercial	Copay card $0	Copay card $5
Medicaid	Can waive copay	
Medicare	If household income under $100,000 will help enroll in NYS EPIC	
No insurance	My Praluent	Repatha Ready

29

University of Rochester Specialty Pharmacy



Late Breaking Study –GAUSS-3

- JAMA April 19,2016
- Randomized clinical trial with truly statin intolerant patients for 24 weeks
- Randomized to Evolocumab vs Ezetimibe
- Ezetimibe had 16.7% LDL reduction
- Evolocumab had 52.8% LDL reduction
- Muscle symptoms reported in 28.8% of Ezetimibe and 20.7% of Evolocumab
- Among statin intolerant patients Evolocumab compared with Ezetimibe resulted in significantly greater reduction in LDL levels after 24 weeks

31

Conclusions

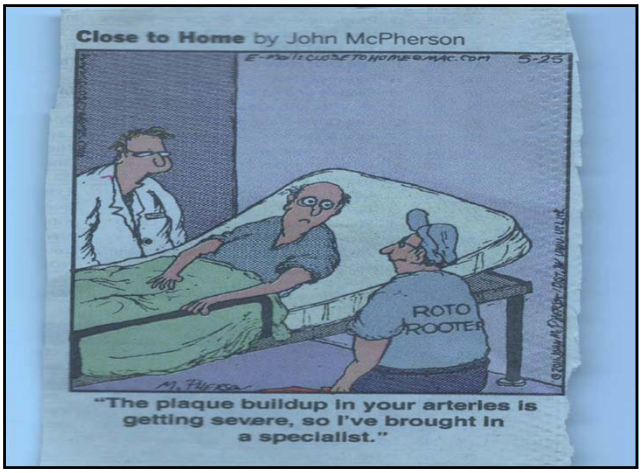
- PCSK9 inhibitors are indicated as add-on therapy to statins and other lipid-lowering therapy in patients with:
  - HeFH or HoFH
  - ASCVD
- Administration is identical for Praluent (alirocumab) and Repatha (evolocumab)
- Careful documentation is critical to obtaining coverage
- Although these are expensive medications, there are multiple options for helping patients obtain them at a reasonable cost

32

Conclusion - continued

- It is good to have 2 drugs in this class with a third possibly coming soon
- This class of drugs has durability – LDL does not rebound with prolonged use
- Well tolerated with low discontinuation rates due to adverse events
- High risk patients should be treated with high intensity statin therapy
- Studies have shown continued benefit the lower the LDL is driven
- PCSK9 inhibitors fill an obvious therapeutic niche in selective high risk patients or statin intolerant patients who are not able to achieve desired LDL levels with conventional treatments

33



UR Medicine

Medicine of the Highest Order