Injectable LDL Lowering Medicines

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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

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?

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

Treatment of FH

• 4 statin benefit groups

- Clinical ASCVD
- Diabetes mellitus, age ≥ 40
- LDL-C ≥ 2 mg/dL
- 7.5% 10-year risk

Benefit Group: Clinical ASCVD

Statin Dose: Moderate-intensity statin

Benefit Group: Diabetes mellitus, age ≥ 40

Statin Dose: Moderate-intensity statin

Benefit Group: LDL-C ≥ 2 mg/dL

Statin Dose: High-intensity statin

Benefit Group: 7.5% 10-year risk

Statin Dose: Moderate-to-high intensity statin
PCSK9 Inhibitors

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

<table>
<thead>
<tr>
<th>Brand</th>
<th>Praluent</th>
<th>Repatha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Alirocumab</td>
<td>Evolocumab</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Sanofi and Regeneron Pharmaceuticals, Inc.</td>
<td>Amgen Inc.</td>
</tr>
<tr>
<td>FDA Approval</td>
<td>July 24th, 2015</td>
<td>August 27th, 2015</td>
</tr>
</tbody>
</table>

PCSK9 Mechanism of Action

- PCSK9 inhibitors reduce LDL Receptor degradation and increase reutilization.

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

Alirocumab clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population (Maximally tolerated statin therapy, LDL not at goal)</th>
<th>Intervention</th>
<th>Mean LDL Change from Baseline at Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH I &amp; FH II (n=735)</td>
<td>FHPII (45% ASCVD)</td>
<td>Alirocumab 75 mg every 14 days vs. placebo</td>
<td>-51% versus +3% with placebo (p&lt;0.0001)</td>
</tr>
<tr>
<td>COMBO I (n=316)</td>
<td>Hyperlipidemia (84% ASCVD)</td>
<td>Alirocumab 75 mg every 14 days vs. placebo</td>
<td>-48% versus -2% with placebo (p&lt;0.0001)</td>
</tr>
<tr>
<td>ODYSSEY LONG TERM (n=2,341)</td>
<td>HeFH and/or ASCVD (69% ASCVD only and 18% HeFH only)</td>
<td>Alirocumab 150 mg every 14 days vs. placebo</td>
<td>-62% versus +1% with placebo (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

ODYSSEY LONG TERM Post Hoc Analysis

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Placebo (%)</th>
<th>Alirocumab (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CHD, including unknown cause</td>
<td>0.9</td>
<td>0.3</td>
<td>0.26</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>2.3</td>
<td>0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Fatal or non-fatal ischemic stroke</td>
<td>0.3</td>
<td>0.6</td>
<td>0.35</td>
</tr>
<tr>
<td>Unstable angina requiring hospitalization</td>
<td>0.1</td>
<td>0.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Composite CV events</td>
<td>3.3</td>
<td>1.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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
### Evolocumab clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population (Maximally tolerated statin ± lipid-lowering therapy, LDL not at goal)</th>
<th>Interventions</th>
<th>Mean LDL Change from Baseline at Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAPLACE-2</td>
<td>Hyperlipidemia (30% ASCVD) Mean baseline LDL: 108 mg/dL</td>
<td>Evolocumab 140 mg every 2 weeks or 420 mg monthly vs. placebo</td>
<td>-64% versus -1% with placebo (p&lt;0.0001) with backgroundatorvastatin 80 mg</td>
</tr>
<tr>
<td>RUTHERFORD-2</td>
<td>HeFH (38% ASCVD) Mean baseline LDL: 156 mg/dL</td>
<td>Evolocumab 140 mg every 2 weeks or 420 mg monthly vs. placebo</td>
<td>-62% versus -1% with placebo (p&lt;0.0001)</td>
</tr>
<tr>
<td>TESLA Part B</td>
<td>HoFH (43% ASCVD) Mean baseline LDL: 162 mg/dL</td>
<td>Evolocumab 420 mg monthly</td>
<td>-23% versus +8% with placebo (P&lt;0.0001)</td>
</tr>
</tbody>
</table>

### 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

### 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?

### 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?

### 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?
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

Highlighted Differences

**Praluent**
- Not indicated for HoFH
- Stable at room temperature for 24 hours
- Option of titrating dose up

**Repatha**
- Indicated for HoFH
- Stable at room temperature for 30 days
- Latex cap and tip

At this time considered clinically equivalent

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**Praluent (alirocumab) and Repatha (evolocumab) Pen Administration**

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

3. Warm to room temp.
4. Prep injection site

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

7. Push and immediately release grey button
8. Keep holding pen against skin until window completely yellow

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*Note: Images and diagrams are not included in this text.*
Praluent (alirocumab) and Repatha (evolocumab) Pen Administration

9. Lift pen straight off skin
10. Discard in sharps container

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

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 then pull out from skin at same angle entered
7. Do not recap. Discard in sharps container.

Administration Troubleshooting

- The button will not push down: Make sure yellow tip is pressed down
- I can’t get the yellow tip to disappear and I’m pressing hard: Pinch your skin to make firm place to inject, then try again
- Round bruises/welts on stomach: Pressing down too hard
- I forgot my injection last week, is it still okay to take? Can give 7 days late
- I left my pen/syringe out of the fridge, is it okay to use? Depends how long: 24 hours for Praluent, 30 days for Repatha
- My pen/syringe froze outside, but it’s thawed now: Can I use it? No!
- I didn’t hear a second click with my pen: Did it work? Yes, as long as the window turned yellow

Cost Concerns

- Each approximately $1,400 per month

<table>
<thead>
<tr>
<th>Insurance</th>
<th>Praluent (alirocumab)</th>
<th>Repatha (evolocumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>Copay card $0</td>
<td>Copay card $5</td>
</tr>
<tr>
<td>Medicaid</td>
<td></td>
<td>Can waive copay</td>
</tr>
<tr>
<td>Medicare</td>
<td>If household income under $100,000 will help enroll in NYS EPIC</td>
<td></td>
</tr>
<tr>
<td>No insurance</td>
<td>My Praluent</td>
<td>Repatha Ready</td>
</tr>
</tbody>
</table>

Available Specialty Medications

- Praluent (alirocumab)
- Repatha (evolocumab)

University of Rochester Specialty Pharmacy

Phone: (585) 273-7504
Fax: (585) 276-1089
Email: specialtypharmacy@urmc.rochester.edu

Pharmacist
Katie Manou, PharmD
Phone: 273-1768
Katherine_Manou@urmc.rochester.edu

Technician
Marquise Melton, CPhT
Phone: 273-1746
Marquise_Melton@urmc.rochester.edu

Cardiology Workflow

- Provider:
  - Sends Prescription to UR Specialty Pharmacy via eRecord (see below), phone 273-4767, or fax 276-1089.
  - If the patient does not have insurance, send MyPraluent or Repatha Ready Intake Form to URMC Specialty Pharmacy via fax 276-1089.

- Specialty Pharmacy:
  - Pharmacist verifies medication regimen, dose, drug interactions, baseline labs, etc.
  - Pharmacist completes prior authorization paperwork and submits to insurance
  - If unable to fill due to insurance network limitations, pharmacist will document alternative preferred pharmacy and route new Rx to provider.

- Specialty Pharmacy – Follow Up:
  - Follow-up phone calls to patient for each refill to discuss administration difficulties, side effects, adherence, monitoring, etc.
  - Available 24/7 for patient concerns and medication questions
  - Any significant changes in patient status will be documented in eRecord as a “Pharmacy Encounter” and routed to provider.

- Prior Authorization Denied:
  - Specialty Pharmacy:
    - Forwards MyPraluent or Repatha Ready Intake Form to coordinate free drug from manufacturer during appeal.
    - Documents in eRecord as “Pharmacy Encounter” and routes to provider.

- Prior Authorization Approved:
  - Specialty Pharmacy:
    - Obtains co-pay assistance through co-pay card for commercially insured patients
    - Enrolls in manufacturer’s assistance program by forwarding MyPraluent or Repatha Ready Intake Form if needed for patients with government-funded insurance
    - Pharmacy technician calls patient to introduce URMC Specialty Pharmacy and coordinate medication delivery to clinic visit, patient’s home, or pick-up at Strong Outpatient Pharmacy.
    - Pharmacist provides medication education, device teaching over the phone or at clinic appointment
    - Pharmacist documents teaching and medication start in eRecord as “Pharmacy Encounter” and routes to provider.
    - Pharmacist orders follow-up LDL in 4-8 weeks after initiation and co-signs to provider

Patient starts therapy
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

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

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