Lipid Management: What’s on the Horizon?

Katie Greenlee, Pharm.D., BCPS, AQ-Cardiology
Cardiology Clinical Specialist
Department of Pharmacy
Cleveland Clinic
No disclosures
Objectives

• Review mechanism of action of new lipid lowering therapy
• Discuss clinical trial data
• Assess their place in therapy
Lipid lowering: Is there an ideal agent?

- Ease of administration / dosing
- Tolerable- low side effect profile
  - Muscle aches
  - Statin intolerance
  - Liver function (LFTs)
- Lack of drug interactions
  - Simvastatin
- Achieves LDL goals
What’s next on the horizon?

- Proprotein convertase subtilisin/kexin 9 (PCSK9) Inhibitors
  - Bococizumab
  - Alirocumab (Praluent™)
  - Evolocumab (Repatha™)
What is PCSK9?

- PCSK9
  - Produced in the liver
  - Binds hepatic LDL receptors and promotes degradation
  - Less LDL cholesterol is then removed by liver
  - Leads to increases in circulating LDL
PCSK9 Inhibitors

- Monoclonal antibody specifically blocks PCSK9 interaction with LDL receptor
  - Prevents degradation of LDL receptor

  - Statins may enhance PCSK9 production
  - May be why doubling statin dose doesn’t double response
PCSK9 Inhibitors

- Cholesterol lowering profile
  - LDL: ~60%
  - Triglycerides: 12-17%
  - Total Cholesterol: 36-37.5%
  - HDL: 4-7%

- Unique dosing- Patient administered
  - Subcutaneous (SubQ) injection
    - Every two weeks
    - Once monthly
# Bococizumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Population</th>
<th>Endpoints / Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of Bococizumab, A monoclonal antibody against proprotein convertase subtilisin/kexsin type 9, from a randomized, placebo-controlled, dose-ranging study with statin-treated subjects with hypercholesterolemia</td>
<td><strong>Primary endpoint:</strong> Absolute change in LDL-C from baseline to 12 weeks after treatment with placebo or bococizumab</td>
<td>N=100 placebo N=251 bococizumab</td>
<td><strong>Efficacy:</strong> LDL-C change from baseline bococizumab 150mg Q14day: -53.4mg/dL (53.1%) 300 mg Q28 day: -44.9mg/dL(41.1%) Up to 44% had dose reductions for LDL-C ≤25 mg/dL</td>
<td>Bococizumab significantly reduced LDL-C Q28 day dosing LDL-C reductions not well maintained between doses “saw tooth” pattern Q14 day dose reduced fluctuations in LDL If no dose reductions LDL lowering may have been</td>
</tr>
<tr>
<td>24 week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2b study</td>
<td><strong>Safety endpoint:</strong> Incidence of adverse events (AEs), serious AEs, laboratory abnormalities, incidence of antidrug antibodies (ADAs), and injections site reactions</td>
<td>Patients with hypercholesterolemia on stable statin therapy with fasting LDL &gt; 80 mg/dL, TGs &lt; 400 mg/dL. Excluded if cardiovascular event in last 6 months</td>
<td><strong>Safety:</strong> AEs similar bococizumab vs placebo: Injection site reaction 0-8% vs 2% Nonserious memory loss: 2 bococizumab patients</td>
<td></td>
</tr>
<tr>
<td>Dose reduction if persistent LDL-C ≤25 mg/dL (after days 43 and 57)</td>
<td></td>
<td>Randomized to: -Q14 day placebo or bococizumab 50, 100, 150 mg -Q28 day placebo or bococizumab 200 or 300 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Am J Cardiol. 2015 May 1;115(9):1212-21
# Alirocumab-Monotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Population</th>
<th>Endpoints / Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ODYSSEY MONO:</strong></td>
<td>Evaluate efficacy and safety of alirocumab monotherapy vs ezetimibe</td>
<td>n= 52 alirocumab&lt;br&gt;n= 51 ezetimibe &lt;br&gt;Hypercholesterolemia with moderate CV Risk*&lt;br&gt;Not receiving statin or other lipid lowering therapy&lt;br&gt;Alirocumab 75 mg Q2wk (increased to 150 mg 2wk 12 if LDL &gt; 70 mg/dL)</td>
<td><strong>Efficacy:</strong>&lt;br&gt;% LDL change from Baseline to 24 weeks:&lt;br&gt;• Alirocumab-54.1%&lt;br&gt;• Ezetimibe-17.2%&lt;br&gt;<strong>Safety:</strong>&lt;br&gt;Muscle related AE:&lt;br&gt;• Alirocumab-2(4 %)&lt;br&gt;• Ezetimibe- 2(4%)&lt;br&gt;CK 10 times ULN:&lt;br&gt;• Alirocumab-0 (0%)&lt;br&gt;• Ezetimibe- 1 (2%)&lt;br&gt;LFT elevation: none&lt;br&gt;Injection site reaction:&lt;br&gt;• Alirocumab- 1(2%)&lt;br&gt;• Ezetimibe- 2(4%)&lt;br&gt;Anti-drug antibodies:&lt;br&gt;• Alirocumab – 6 (12%)</td>
<td>Alirocumab showed greater LDL –C reduction vs ezetimibe&lt;br&gt;Alirocumab 75 mg Sub q 2 weeks ≥50% LDL-C reduction in most patients&lt;br&gt;Ldl &lt;25 mg/dL in 3 patients with no safety concerns observed</td>
</tr>
</tbody>
</table>

* Moderate cardiovascular risk (CV) 10 yr risk of fatal CV events ≥1% and ≤ 5%
### Alirocumab- Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Population</th>
<th>Endpoints /Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol</strong>&lt;br&gt;3 separate phase 1 clinical studies:&lt;br&gt;Single dose studies&lt;br&gt;• Intravenous&lt;br&gt;• Subcutaneous&lt;br&gt;Multiple dose study&lt;br&gt;• 50, 100, 150 mg alirocumab or placebo days 1, 29, and 43</td>
<td><strong>Primary outcome:</strong>&lt;br&gt;• Incidence and severity of treatment-emergent adverse events&lt;br&gt;<strong>Secondary outcome:</strong>&lt;br&gt;• Effect on lipid profile</td>
<td>Multiple dose study:&lt;br&gt;<strong>Atorvastatin arms with LDL &gt; 100mg/dL:</strong>&lt;br&gt;N= 21 Heterozygous familial hypercholesterolemia&lt;br&gt;N= 30 non-familial hypercholesterolemia&lt;br&gt;<strong>Modified diet and LDL &gt; 130 mg/dL arm:</strong>&lt;br&gt;N= 10 non-familial hypercholesterolemia</td>
<td>No serious adverse events in multiple dose study&lt;br&gt;&lt;br&gt;&lt;b&gt;Safety in all 3 studies:&lt;/b&gt;&lt;br&gt;• No LFTS &gt; 3 x ULN&lt;br&gt;• No creatinine elevations &gt; 1.7 mg/dL&lt;br&gt;• 5/39 (13%) alirocumab + atorvastatin group creatine kinase (CK) elevation &gt; 3 ULN&lt;br&gt;• No CK &gt;10 ULN&lt;br&gt;&lt;br&gt;&lt;b&gt;Lipid profile effect:&lt;/b&gt;&lt;br&gt;In 50, 100, 150 mg groups on atorvastatin&lt;br&gt;LDL lowered to: 77.5, 61.3, 53.8 mg/dL or (39.2%, 53.7%, 61.0% reduction)</td>
<td>LDL lowering response similar between familial and non-familial.&lt;br&gt;Maximal lowering seen in 2 weeks&lt;br&gt;Safety profile information limited due to short treatment duration&lt;br&gt;CK elevations were brief</td>
</tr>
</tbody>
</table>
# Alirocumab: Long Term Study

## Objectives

**Primary efficacy endpoint:**
- % change in LDL cholesterol from baseline to 24 weeks

**Safety endpoints:**
- Adverse events
- Symptoms
  - Abnormalities in Lab
  - Vital signs
  - EKG
- Adjudicated cardiovascular events

**Post Hoc:** major adverse cardiovascular events (composite of death from any coronary heart disease (CHD), non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization)

## Population

- **N= 1553** alirocumab 150mg sub Q every 2 weeks
- **N=788** placebo
- 2:1 Randomization
- Double blind
- Every 2 weeks for 78 weeks in addition to statin therapy

## Efficacy:

- **Mean % change LDL**
  - Alirocumab vs Placebo
  - 61.0% vs 0.8%

## Safety:

- **Alirocumab vs Placebo**
  - Injection site reactions (5.9 vs 4.2%)
  - Myalgias (5.4 vs 2.9%)
  - Neurocognitive events (1.2 vs 0.5%)
    - Amnesia n=5
    - Memory impairment n=4
    - Confusional state n=4

## Conclusions

- Alirocumab compared to placebo reduced LDL by 62% at 24 weeks

- Post hoc safety analysis rate of adverse CV events 48% lower for alirocumab vs placebo.

- With all CV events included (CHF requiring hospitalization, ischemia driven revascularization), difference became non significant

---

**N Engl J Med. Published online 3/15/2015**
## Evolocumab-Statin Intolerance

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Population</th>
<th>Endpoints Results</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| GAUSS-2     | **Co-Primary endpoints:** % change for baseline LDL-C at mean of weeks 10-12 and at week 12  
**Safety endpoint:** Treatment emergent and serious adverse events, CK and hepatic enzyme elevations, and anti-evolocumab antibodies | N= 205 evolocumab  
N= 102 ezetimibe  
Baseline LDL-C 193 ± 59 mg/dL  
Patient on no or low-dose statin above NCEP ATP III* goals with intolerance ≥ 2 statins**  
Randomization (placebo controlled)  
• Evolocumab 140 mg Q2 weeks  
• Evolocumab 420 mg once monthly  
• Ezetimibe 10 mg daily | **Efficacy:** Mean LDL-C reduction from baseline at mean of 10-12 weeks  
• 56.1% -140mg Q2wk  
• 55.3% - 240mg Q M  
36.9%, 38.7% reduction- ezetimibe groups  
Mean at 12 weeks similar  
**Safety:**  
Myalgia  
8% evolocumab  
18% ezetimibe (more likely to develop if on low-dose statin) | Evolocumab reduced LDL-C in patients with statin intolerance  
Evolocumab may be useful for in hypercholesterolemic patients with intolerance to current agents as there was low incidence of muscle related side effects  
**Limitations:** Absence of blinded statin re-challenge group |

* National Cholesterol Education Program Adult Treatment Panel  
** Inability to tolerate any dose of statin or increase dose above smallest tablet strength because of muscle-related side effects  

J Am Coll Card 2014;63:2541-8
## Evolocumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Population</th>
<th>Endpoints Results</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| PCSK9 inhibition with evolocumab (AMG145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial | **Co-Primary endpoints:** % change in plasma LDL from baseline to week 12 and at mean of 10-12 weeks.  
**Secondary endpoints:** Absolute change from baseline in LDL and % of patients achieving target LDL lower than 1.8 mmol/L at same timepoints | **Evolocumab** N=110 (140mg q2 week Sub Q)  
N= 110 (420 mg q M Sub Q)  
**Placebo** N= 54 (q 2 weeks SubQ)  
N= 55 (q M Sub Q) | **Efficacy:**  
Mean LDL-C reduction from baseline at mean of 10-12 weeks  
Evolocumab vs placebo  
Q 2wk: 60.2%  
Q M: 65.6%  
**Mean reduction at 12 weeks**  
Q 2wk: 59.2%  
Q M: 61.3%  
**Safety:**  
Evolocumab vs placebo:  
Nasopharyngitis: 9% vs 5%  
Muscle related: 5% vs 1% | In patients with heterozygous familial hypercholesterolemia, evolocumab reduced LDL by 60%  
LDL of 1.8 mmol/L achieved in more than 60% of patients  
Well tolerated |

1.8 mmol/L = 70 mg/dL  

LANCET 2015;385:331-40
# Evolocumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Population</th>
<th>Endpoints Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSLER</td>
<td><strong>Primary endpoint:</strong> Incidents of adverse events&lt;br&gt;<strong>Secondary endpoint:</strong> % change in LDL&lt;br&gt;Pre-specified exploratory outcome (adjudicated events): Cardiovascular events (death, MI, UA, coronary revascularization, stroke, TIA, and heart failure</td>
<td>N=2976 evolocumab plus standard therapy&lt;br&gt;N=1489 standard therapy&lt;br&gt;Enrolled after participation in one of 12 phase 2 or 3 “parent trials” for 12 weeks&lt;br&gt;Followed for median of 11.1 months&lt;br&gt;Evolocumab either: 140 mg Sub Q Q2wks&lt;br&gt;420 mg Sub Q q Month</td>
<td><strong>Safety:</strong> Evolocumab vs standard:&lt;br&gt;  - LFTs 1.0% vs 1.2%&lt;br&gt;  - CK 0.6% vs 1.1%&lt;br&gt;  - Neurocognitive 0.9% vs 0.3%&lt;br&gt;  - Injection site reaction: 4.3% evolocumab&lt;br&gt;<strong>Efficacy:</strong> Evolocumab vs standard:&lt;br&gt;  - LDL reduction 61% at 12 weeks&lt;br&gt;  - LDL reduced to 100 mg/dL 90.2% vs 26.0%&lt;br&gt;  - LDL reduced to 70 mg/dL 73.6% vs. 3.8%&lt;br&gt;</td>
<td>Reduction in LDL by 61% at 12 weeks --sustained at 11 months&lt;br&gt;Evidence of reduction in cardiovascular events at one year&lt;br&gt;  - Evolocumab vs standard: 0.95% vs 2.18 %&lt;br&gt;  - HR 0.47; 95%CI 1.28-0.78&lt;br&gt;<strong>Limitations</strong>&lt;br&gt; --open label may have influenced reporting of events&lt;br&gt; --#of events small&lt;br&gt; --patients enrolled in trial only if no adverse events in “parent trials” --12 weeks on study drug already</td>
</tr>
</tbody>
</table>

N Engl J Med. Published online 3/15/2015
Further Considerations

• Outcome data still ongoing
  - SPIRE I and II (bococizumab)
    • I- whether lowering LDL to below recommended targets will lead to further reduced cardiovascular outcomes
    • II- efficacy and safety in high risk patients not at target (<100mg/dL) on high dose statin or statin intolerant
  - ODYSSEY OUTCOMES (alirocumab) will assess CV benefit over 5 years
  - FOURIER study (evolocumab) full assessment of cardiovascular outcomes (5 years)
Further Considerations

• Neurologic events to be further evaluated
• How low is too low for LDL?
• Cost?
• Future directions:
  - Potential oral options for small molecule PCSK9 inhibitors
    • Human trials (phase I) soon
Conclusions

- PCSK9 inhibitors lower LDL by ~60%
- Useful for patient with familial hypercholesterolemia
- Potential option for statin intolerance
- Outcome data ongoing
- FDA biologics application license submission
  - Alirocumab- July
  - Evolocumab- August
  - Bococizumab- To be determined
Cleveland Clinic

Every life deserves world class care.