Novel Therapeutics in Dyslipidemia

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Advances in Genetic Technology/Drug Development

• The PCSK9 gene as a regulator of plasma LDL-C was found in studies of human genetics.
• Abifadel et al studied large pedigree and discovered that gain-of-function mutations in PCSK9 led to autosomal dominant familial hypercholesterolemia.
• Cohen et al showed that individuals with nonsense mutations in PCSK9 had lower cholesterol and LDL-C compared to those without the mutation.
• Subsequently, there has been development of novel therapies related to PCSK9 inhibition.

The Role of PCSK9 in the Regulation of LDLR Expression

PCSK9-Mediated Degradation of LDLR

PCSK9 inhibitors

- Two FDA approved PCSK9 inhibitors
- Alirocumab (Praluent) and Evolocumab (Repatha)
- Praluent is a PCSK9 inhibitor antibody indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C)
- The effect of Praluent on cardiovascular morbidity and mortality has not been determined.
• Repatha is a PCSK9 inhibitor antibody indicated as an adjunct to diet and:
  – Maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
  – Other LDL-lowering therapies (e.g. statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
  – The effect of REPATHA on cardiovascular morbidity and mortality has not been determined.
  – COST ~$14,000
Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events


Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

- Major adverse cardiovascular events was lower with alirocumab (1.7%) than with placebo (3.3%) in a post hoc analysis
  (HR 0.52; 95% confidence interval, 0.31 to 0.90; nominal P = 0.02).

- (MACE consists of death from coronary heart disease, non fatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization)


<table>
<thead>
<tr>
<th>Study</th>
<th>Population Eligible for Study</th>
<th>Study Interventions/Duration</th>
<th>Age, Gender, Ethnicity</th>
<th>Other population characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blom, 2014 DESCARTES N=901</td>
<td>Hyperlipidemia and LDL-C ≥ 75 mg/dL</td>
<td>Subcutaneous evolocumab 420 mg or placebo every 4 weeks/48 weeks</td>
<td>Age: 56 years Female: 52.3% White: 80.4%</td>
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<tr>
<td>Cannon, 2015 ODYSSEY COMBO II N=720</td>
<td>Hypercholesterolemia.C VO and LDL-c ≥70 mg/dL, or no history of CVD but at high cardiovascular risk and LDL-C ≥100 mg/dL.</td>
<td>Subcutaneous alirocumab 75 mg every 2 weeks or ezetimibe 10 mg daily (both with statins)/104 weeks</td>
<td>Age: 61.5 years Female: 26.4% White: 84.7%</td>
<td>CHD: 60.1% LDL-C: 106 mg/dL HDL-C: 48 mg/dL High-intensity statin: 66.7%</td>
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<td>Giugliano, 2012 Desai, 2014 LAPLACE-TIMI 57 N=831</td>
<td>Hypercholesterolemia while on statin with LDL-C=85 mg/dL</td>
<td>Subcutaneous evolocumab 70 mg, 105 mg, 140 mg, or placebo every 2 weeks or 280 mg, 350 mg, 420 mg or placebo every 4 weeks/12 weeks</td>
<td>Age: 82 years Female: 51.0% White: 89.0%</td>
<td>CAD: 30.0% LDL-C: 123 mg/dL HDL-C: 54 mg/dL</td>
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<td>Hirayama, 2014 YUKAWA N=310</td>
<td>Hypercholesterolemia (high risk for cardiovascular events).</td>
<td>Subcutaneous evolocumab 70 mg, 140 mg every 2 weeks, 280 mg, 420 mg every 4 weeks or placebo/12 weeks</td>
<td>Age: 61.5 years Female: 37.1%</td>
<td>CAD: 25.1% LDL-C: 139 mg/dL HDL-C: 54 mg/dL Intensive statin: 6.2%</td>
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<td>Kereiakes, 2015 ODYSSEY COMBO 1 N=316</td>
<td>Hypercholesterolemia. LDL-C&gt;70 mg/dL and established CVD or LDL-C=100 mg/dL, with CHD risk equivalents</td>
<td>Subcutaneous alirocumab 75 mg every 2 weeks or placebo/52 weeks</td>
<td>Age: 63 years Female: 54.2% White: 81.6%</td>
<td>CHD: 78.2% LDL-C: 98 mg/dL HDL-C: 49 mg/dL High-intensity statin: 62.7% Ezetimibe: 8.2%</td>
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<td>McKinney, 2012 N-183</td>
<td>Patients with LDL-C ≥ 100 mg/dL on stable dose atorvastatin 10 mg, 20 mg, or 40 mg for ≥ 8 weeks</td>
<td>Subcutaneous alirocumab 50 mg, 100 mg, 150 mg every 2 weeks; 200 mg, 300 mg every 4 weeks or placebo/12 weeks</td>
<td>Age: 57 years Female: 52.5% White: 86.3%</td>
<td>CAD: 5.5%</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Intervention</td>
<td>Duration</td>
<td>Age</td>
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<tr>
<td>Steen, 2012</td>
<td>N=77</td>
<td>Heterozygous familial hypercholesterolemia LDL-C=100 mg/dl</td>
<td>Subcutaneous alirocumab 150 mg, every 4 weeks or every 2 weeks, or placebo/12 weeks</td>
<td>53.4 years</td>
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<tr>
<td>Steen, 2012</td>
<td>N=61</td>
<td>Heterozygous and nonheterozygous familial hypercholesterolemia</td>
<td>Subcutaneous alirocumab 50 mg, every 4 weeks or every 2 weeks, or placebo/12 weeks</td>
<td>52.8 years</td>
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<td>Stroes, 2014</td>
<td>N=307</td>
<td>Statin intolerant to &gt; 2 statins LDL-C &gt; NCEP ATP III goal</td>
<td>Ezetimibe daily+ placebo every 2 weeks, evolocumab 280 mg every 2 weeks + placebo daily, ezetimibe daily + placebo monthly, evolocumab 420 every 4 weeks + placebo daily/12 weeks</td>
<td>61.5 years</td>
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<td>Sullivan, 2012</td>
<td>N=160</td>
<td>Statin intolerant at least 1 statin</td>
<td>Evolocumab 280 mg, 350 mg, and 420 mg, every 4 weeks or every 2 weeks with ezetimibe 10 mg; ezetimibe 10 mg + placebo (all administered subcutaneously every 4 weeks/12 weeks)</td>
<td>61.8 years</td>
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PCSK9: rapid progress from discovery to clinic in less than a decade

Monoclonal Antibodies Nomenclature and Safety Considerations
Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease

JAMA 2016; 316(7):743-753

J Clin Lipid. 2016 Jan-Feb;10(1 Suppl):S1-43
Mipomersen

- Antisense therapeutic that targets messenger RNA for apolipoprotein B
- Administered as a weekly injection for homozygous familial hypercholesterolemia
- LDL-C decreases by 25%
- Boxed warning of liver toxicity and requires certification by the prescriber and pharmacy

Lomitapide

- Inhibits the microsomal triglyceride transfer protein (MTP) which is necessary for VLDL assembly and secretion in the liver
- Side effects- leads to elevated aminotransferase and fat accumulation in the liver
- FDA approved in homozygous familial hypercholesterolemia to reduce LDL-C, Tchol, apoB and non-HDL
Crosby et al described a rare loss-of-function and missense mutation in APOC3, where carriers of rare APOC3 mutations had substantially lower serum triglyceride (39%) and higher HDL and lower LDL-C, with subsequently a 40% reduction in developing cardiovascular disease.

- Potentially revolutionary drugs related to APOC3 are in development.


Advances in Genetic Technology

- Traditionally genes that cause disorders identified by linkage analysis
- The nearer two genes are on a chromosome, the lower the chance of a recombination event, or “swap”, occurring between them, and the more likely they are to be inherited together.

ApoCIII

- Apolipoprotein C-III (ApoC-III) is a small protein that resides on various lipoproteins
- Inhibits lipoprotein hepatic lipases
- Impairs hepatic uptake of triglyceride (TG)-rich lipoproteins (such as lipoprotein remnants)
- Generally promotes hypertriglyceridemia.
- May contribute to insulin resistance
- May contribute to atherosclerosis.
Next Generation Sequencing

- Allows for multi-gene panels and whole exome sequencing of all coding regions of an affected individual.
- Linkage between phenotype and genotype is tested

Rare variants

- Rare variant association studies target the class of genetic variation with frequencies less than 1%.
- Using next generation sequencing, coupled with targeted capture of the protein-coding regions (“exome sequencing”), rare alleles responsible for Mendelian diseases have been discovered.
- Rare variants can provide evidence for new pathways in disease biology and uncover new targets for therapy (i.e. PCSK9)