Inhibition of PCSK9: The Birth of a New Therapy

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Disclosures

Dr. Kastelein consults with and speaks for biotechnological as well as pharmaceutical companies that develop molecules that influence lipoprotein metabolism and/or inflammation to prevent CVD, including Regeneron, Sanofi, Amgen, Roche, Pfizer, and Eli Lilly.
Novel Approaches to Modify Lipids and Lipoproteins

- Low Density Lipoprotein
- High Density Lipoprotein
- Triglyceride Rich Lipoproteins
- Inflammation
- Lipoprotein a
New Approaches to LDL Reduction

What is in development?

• Cholesterol Absorption Inhibitors
• Squalene Synthase (SSI) inhibitors
• Apo B mRNA antisense drugs
• Microsomal Triglyceride Transfer Protein (MTP) inhibitors
• Thyroxin Receptor Agonists
• PCSK9 Inhibitors
LDL-Receptor Function and Life Cycle
The Role of PCSK9 in the Regulation of LDL Receptor Expression
LDL-C Reduction and Coronary Events

Lancet 2005; 366: 1267–78

14 Trials
90,056 patients

Proportional Reduction in Events

Reduction in LDL-C (mmol/L)
Adapted from Cohen JC. N Engl J Med 2006;354:1264-72; ARIC=Atherosclerosis Risk in the Community
Loss of Function PCSK9 Mutations

- Only a small number of patients who are homozygous (or compound heterozygotes) for PCSK9 have been discovered and studied.

- These patients appear to have:
  - Very low LDL-C levels (~10-20 mg/dL)
  - Relatively low TG levels
  - Normal HDL-C levels

- These patients have no other health problems
Familial Hypercholesterolemia
Familial Hypercholesterolemia

Age of onset of coronary atherosclerosis in FH heterozygotes as assessed by angiography

**FH in the Netherlands:**
Screening between January 1994 and December 2010

- **Referred HeFH patients:** 2400
- **Screened family members:** 33,041
  - **Family members with HeFH:** 11,783
    - TC: 9.72 mmol/L
  - **Family members without HeFH:** 21,259
    - TC: 6.15 mmol/L
FH in the Netherlands: Screening between January 1994 and December 2010

- Referred HeFH patients: 2400
- Screened family members: 33,041
- Family members with HeFH: 11,783
- Family members without HeFH: 21,259
- OR: 12.8 [95% CI: 6.2 – 26.5]
FH Patients at LDL Goal

[Graph showing LDL-C target attainment vs. mmol/L and mg/dL]

Pijlman AH. Atherosclerosis 2010;209:189-94
Impact of a SAR236553/REGN727 on LDL Receptor Expression
The Use of a PCSK9 Monoclonal AB in heFH Patients

A Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to PCSK9, REGN727/SAR236553, in Patients with Heterozygous Familial Hypercholesterolemia on Stable Statin Dose With or Without Ezetimibe Therapy

The Use of a PCSK9 Monoclonal AB in heFH Patients

- The goal of this Phase II trial was to evaluate the LDL-C efficacy and safety of REGN727/SAR236553 in:
  - A larger population
  - More diverse HeFH population in terms of LDLr defects
  - More severely affected and aggressively treated group of HeFH patients, including those with CAD
  - Assess multiple and higher doses combined with different dosing regimens of REGN727/SAR236553
The Use of a PCSK9 Monoclonal AB in heFH Patients

Run-in/Screening Period (1–7 weeks)

Treatment Period (12 weeks)

- N=15: Placebo Q2W
- N=15: REGN727 150 mg Q4W w/alt PBO
- N=16: REGN727 200 mg Q4W w/alt PBO
- N=15: REGN727 300 mg Q4W w/alt PBO
- N=16: REGN727 150 mg Q2W

Follow-up Period (8 weeks)

Primary Endpoint
% Δ calculated LDL-C from baseline to week 12

WK -1 LDL-C ≥ 100 mg/dL (2.6 mmol/L) on stable statin dose ± ezetimibe for ≥6 wks

Diet
- W-7 V1
- W-1 V1a
- W0 V2
- W2 V3
- W4 V4
- W6 V5
- W8 V6
- W10 V7
- W12 V8
- W16 V9
- W20 V10
The Use of a PCSK9 Monoclonal AB in heFH Patients

<table>
<thead>
<tr>
<th>Number of randomized patients</th>
<th>77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>53.4 years</td>
</tr>
<tr>
<td>Female</td>
<td>39.0%</td>
</tr>
<tr>
<td>White race</td>
<td>94.8%</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>41.6%</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>3.9%</td>
</tr>
<tr>
<td>‘High-dose’ statin treatment*</td>
<td>76.6%</td>
</tr>
<tr>
<td>Ezetimibe treatment</td>
<td>71.4%</td>
</tr>
</tbody>
</table>

*atorvastatin 40 mg/80 mg; rosuvastatin 20 mg/40 mg; simvastatin 80 mg.
The Use of a PCSK9 Monoclonal AB in heFH Patients: Results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline LDL-C mg/dL [mmol/L]</th>
<th>% Change LDL-C&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>150.8 [3.9]</td>
<td>−10.7 (5.0)</td>
</tr>
<tr>
<td>REGN727 150 mg Q4W</td>
<td>166.7 [4.3]</td>
<td>−28.9 (5.1)*</td>
</tr>
<tr>
<td>REGN727 200 mg Q4W</td>
<td>169.8 [4.4]</td>
<td>−31.5 (4.9)*</td>
</tr>
<tr>
<td>REGN727 300 mg Q4W</td>
<td>139.6 [3.6]</td>
<td>−42.5 (5.1)*</td>
</tr>
<tr>
<td>REGN727 150 mg Q2W</td>
<td>147.2 [3.8]</td>
<td>−67.9 (4.9)*</td>
</tr>
</tbody>
</table>

<sup>*P</sup>&lt;0.0001 for % change REGN727 vs. Placebo.

<sup>1</sup>LS mean (SE), using LOCF method.

Stein EA et al. Lancet on-line May 26, 2012
The Use of a PCSK9 Monoclonal AB in heFH Patients: Results
The Use of a PCSK9 Monoclonal AB in heFH Patients: Goal Attainment

Stein EA et al. Lancet on-line May 26, 2012
The Use of a PCSK9 Monoclonal AB in heFH Patients: Secondary Results

Stein EA et al. Lancet on-line May 26, 2012
The Use of a PCSK9 Monoclonal AB in heFH Patients: Safety

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=15)</th>
<th>150 mg Q4W (n=15)</th>
<th>200 mg Q4W (n=16)</th>
<th>300 mg Q4W (n=15)</th>
<th>150 mg Q2W (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatinine, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Mean [SD])</td>
<td>0.7 (0.1)</td>
<td>0.9 (0.1)</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.2)</td>
<td>1.0 (0.2)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.7 (0.1)</td>
<td>0.8 (0.1)</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.2)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>Week 12</td>
<td>0.7 (0.1)</td>
<td>0.8 (0.1)</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.2)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td><strong>Glucose, mg/dL</strong></td>
<td>98.7 (10.7)</td>
<td>98.5 (8.5)</td>
<td>102.6 (18.2)</td>
<td>95.1 (6.9)</td>
<td>104.1 (15.1)</td>
</tr>
<tr>
<td>(Mean [SD])</td>
<td>98.7 (7.7)</td>
<td>95.6 (9.2)</td>
<td>98.4 (18.9)</td>
<td>95.9 (11.8)</td>
<td>101.8 (11.7)</td>
</tr>
<tr>
<td>Baseline</td>
<td>98.7 (10.7)</td>
<td>98.5 (8.5)</td>
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<td>101.8 (11.7)</td>
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<tr>
<td><strong>ALT, IU/L &gt;3x ULN, n</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>AST, IU/L &gt;3x ULN, n</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Creatinine kinase, IU/L &gt;3x ULN, n</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>hsCRP mg/L, (Median [Q1;Q3])</strong></td>
<td>0.9 (0.4; 1.6)</td>
<td>0.6 (0.3; 1.4)</td>
<td>0.7 (0.5; 2.5)</td>
<td>0.7 (0.5; 1.3)</td>
<td>1.4 (0.6; 3.4)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.7 (0.4; 1.2)</td>
<td>0.4 (0.3; 1.4)</td>
<td>0.7 (0.5; 1.3)</td>
<td>0.6 (0.4; 1.7)</td>
<td>1.0 (0.7; 3.7)</td>
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<td>0.6 (0.4; 1.7)</td>
<td>1.0 (0.7; 3.7)</td>
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hsCRP=high sensitivity C-reactive protein; PBO=Placebo.

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The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients

LAPLACE-TIMI 57 Primary Results

A Double-blind, Randomized, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of a Monoclonal Antibody to PCSK9 in Combination with a Statin in Patients with Hypercholesterolemia

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Brigham and Women’s Hospital
Harvard Medical School, Boston, MA

Supported by research grant from Amgen, Inc.
The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients

- A global, randomized, double-blind, phase 2 trial
- Patients
  - 18–80 years
  - On stable dose of statin ± ezetimibe
  - LDL-C ≥ 85 mg/dL
The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients: Results

Mean % Change in UC LDL-Cholesterol (SE) at Week 12 Compared to Placebo

AMG 145 Q2W
- 70mg (n=30)  
- 105mg (n=39)  
- 140mg (n=40)  

AMG 145 Q4W
- 280mg (n=35)  
- 350mg (n=37)  
- 420mg (n=46)  

P<0.001 for each AMG 145 dose v. placebo
The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients: Results

NCEP High Risk Patients in LAPLACE-TIMI 57
Treated with 140mg Q2W AMG 145 mean (SD):
1.3 mmol/l

NCEP High Risk Patients in LAPLACE-TIMI 57 at Baseline mean (SD):
123 (30) mg/dL
Conclusion

In the next five years, we will prove or disprove that additional LDL lowering with other agents than statins is effective and we will show or not show that the HDL hypothesis is true.