Inflammation as a Target for Therapy in Atherothrombosis

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Brigham and Women’s Hospital, Boston MA

ESC London PACE 2015
Cytokines and Cardiovascular Disease: Exploring Inflammation & Clinical Outcomes
Inflammation in atherosclerosis: from pathophysiology to practice

Libby P, Ridker PM, Hansson GK. JACC 2009;54:2129-38
Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?
INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

PAUL M. RIDKER, M.D., MARY CUSHMAN, M.D., MEIR J. STAMPFER, M.D., RUSSELL P. TRACY, PH.D., and CHARLES H. HENNEKENS, M.D.
The magnitude of independent risk associated with inflammation is at least as large, if not larger, than that of BP and cholesterol.

<table>
<thead>
<tr>
<th>Risk Ratio (95%CI) per 1-SD higher usual values</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>1.37 (1.27-1.48)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.35 (1.25-1.45)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.16 (1.06-1.28)</td>
</tr>
<tr>
<td>Non-HDLC</td>
<td>1.28 (1.16-1.40)</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, smoking, diabetes, BMI, triglycerides, alcohol, lipid levels, and hsCRP.
JUPITER

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Number Needed to Treat (NNT₅) = 25

Ridker et al NEJM 2008;359:2195-2207
JUPITER

Achieved LDLC, Achieved hsCRP, or Both?

The **Real Controversy:**

Is the large benefit observed in the JUPITER trial due to lipid lowering, to inflammation inhibition, or to a combination of these two processes?
Targeting Inflammatory Pathways for the Treatment of Cardiovascular Disease

Vessel Wall
- 5-LO Inhibitors
- FLAP Inhibitors
- Anti-CAMs
- SIRT activators
- CCR2 CCR5 Antagonists

Macrophage/Monocyte
- Leukotriene Function
- MMP-9
- Monocyte Recruitment
- ICAM-1
- VCAM
- P-selectin
- E-selectin
- Lp-PLA2
- sPLA2
- CRP

Adipose Tissue
- Adalimumab
- Infliximab
- Tocilizumab
- Low Dose Methotrexate

NLRP3 Inflammasome
- TNF-α
- IL-1β
- IL-18
- Canakinumab
- Anakinra
- Colchicine

Upstream Targets and Biomarkers

Liver
- CRP RNA - Antisense Anti-CRPs
- PAI-1
- Fibrinogen
- SAA

Downstream Targets and Biomarkers

Vascular risk hsCRP (mg/L)
- High: > 3 mg/L
- Intermediate: 1-3 mg/L
- Low: < 1 mg/L
IL-6 and Risk of Future MI in Apparently Healthy Men

$P$ Trend = 0.001

Ridker et al, Circulation 2000;101:1767-1772
Mendelian Randomization and the IL-6 Regulatory Pathway

Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies

IL6R Genetics Consortium and Emerging Risk Factors Collaboration*  

**Summary**  
**Background** Persistent inflammation has been proposed to contribute to various stages in the pathogenesis of cardiovascular disease. Interleukin-6 receptor (IL6R) signalling propagates downstream inflammation cascades. To assess whether this pathway is causally relevant to coronary heart disease, we studied a functional genetic variant known to affect IL6R signalling.

The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis

The Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium*  

**Summary**  
**Background** A high circulating concentration of interleukin 6 is associated with increased risk of coronary heart disease. Blockade of the interleukin-6 receptor (IL6R) with a monoclonal antibody (tocilizumab) licensed for treatment of rheumatoid arthritis reduces systemic and articular inflammation. However, whether IL6R blockade also reduces risk of coronary heart disease is unknown.
Effects of Polymorphism in the IL-6 Receptor Signaling Pathway On Downstream CRP Levels and Risks of Coronary Heart Disease

Sawar N et al, Lancet 2012;379;1205-13
Swerdlow et al, Lancet 2012;379;1214-24
Testing the Inflammatory Hypothesis of Atherothrombosis: Do we attack the biomarker or attack the process?
## Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

<table>
<thead>
<tr>
<th></th>
<th>Statins</th>
<th>TNF Inhibition</th>
<th>IL-6 Inhibition</th>
<th>LDM</th>
<th>IL-1β Inhibition</th>
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<tr>
<td>TC</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>←−−→</td>
<td>←−−→</td>
</tr>
<tr>
<td>LDL</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>←−−→</td>
<td>←−−→</td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>←−−→</td>
<td>←−−→</td>
</tr>
<tr>
<td>TG</td>
<td>←−−→</td>
<td>↑</td>
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<tr>
<td>Chylo</td>
<td>←−−→</td>
<td>↑</td>
<td>↑</td>
<td>←−−→</td>
<td>←−−→</td>
</tr>
<tr>
<td>CRP / IL-6</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
For More Information:
theCIRT.org theCANTOS.org
To directly test the inflammatory hypothesis of atherothrombosis

To evaluate in a randomized, double-blind, placebo-controlled trial whether MTX given at a target dose of 20 mg po weekly over a three year period will reduce rates of recurrent myocardial infarction, stroke, or cardiovascular death among patients with a prior history of myocardial infarction and either type 2 diabetes or metabolic syndrome.

N = 7,000  NHLBI-Sponsored
Enrollment to Start June 2013
350 US and Canadian Sites
Methotrexate Inhibits Atherogenesis in Cholesterol-fed Rabbits

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14
## LDM and CVD: Observational Evidence

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>HR* (95 % CI)</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wichita</td>
<td>RA</td>
<td>0.4 (0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td>Choi 2002</td>
<td></td>
<td>0.3 (0.2 - 0.7)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4 (0.3 – 0.8)</td>
<td>CV Mortality</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>Netherlands</td>
<td>RA</td>
<td>0.3 (0.1 – 0.7)</td>
<td>CVD</td>
<td>LDM only</td>
</tr>
<tr>
<td>van Helm 2006</td>
<td></td>
<td>0.2 (0.1 – 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 – 1.2)</td>
<td>CVD</td>
<td>LDM + HCQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 – 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ + HCQ</td>
</tr>
<tr>
<td>Miami VA</td>
<td>PsA</td>
<td>0.7 (0.6 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Pradanovich 2005</td>
<td></td>
<td>0.5 (0.3 – 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>0.8 (0.7 – 1.0)</td>
<td>CVD</td>
<td>LDM</td>
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<tr>
<td></td>
<td></td>
<td>0.6 (0.5 – 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
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<tr>
<td>CORRONA</td>
<td>RA</td>
<td>0.6 (0.3 – 1.2)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Solomon 2008</td>
<td></td>
<td>0.4 (0.2 – 0.8)</td>
<td>CVD</td>
<td>TNF-inhibitor</td>
</tr>
<tr>
<td>QUEST-RA</td>
<td>RA</td>
<td>0.85 (0.8 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Narango 2008</td>
<td></td>
<td>0.82 (0.7 – 0.9)</td>
<td>MI</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.89 (0.8 – 1.0)</td>
<td>Stroke</td>
<td>LDM</td>
</tr>
<tr>
<td>UK Norfolk</td>
<td>RA, PsA</td>
<td>0.6 (0.4 – 1.0)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td>0.5 (0.3 – 1.1)</td>
<td>CV Mortality</td>
<td>LDM</td>
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Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

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<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
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</table>
The Balance of IL-1 and IL-1Ra: Key Regulatory Proteins for Innate Immunity
NLRP3 Cryopyrin Inflammasome, Caspase-1, and IL-1β Maturation
Endogenous Danger Signals in Vascular Biology?

Multiple Pathways of Activation

Cholesterol crystals
Duewell / Latz  Nature 2010

Atheroprone Flow
Xiao / Shyy  Circulation 2013

Hypoxia
Folco / Libby  Circ Res 2014

NETS (Neutrophil Extracellular Traps)
Warnatsch  Science 2015
Canakinumab (Ilaris, Novartis)

- high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)
- designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine
- long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months
Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

A Phase IIb Randomized, Placebo-Controlled Trial

Paul M Ridker, MD, MPH; Campbell P. Howard, MD; Verena Walter, Dipl Math (FH); Brendan Everett, MD; Peter Libby, MD; Johannes Hensen, MD; Tom Thuren, MD, PhD, on behalf of the CANTOS Pilot Investigative Group

Canakinumab Dose (mg/month)

- Fibrinogen
- Interleukin-6
- C-reactive Protein

Median Reduction (%)

Ridker PM, et al; Circulation 2012; 126:2739-2748
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) (Ridker PI)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation of hsCRP (> 2 mg/L)

Randomized Canakinumab 50 mg SC q 3 months
Randomized Canakinumab 150 mg SC q 3 months
Randomized Canakinumab 300 mg SC q 3 months
Randomized Placebo SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death

Secondary Endpoints: Total Mortality, New Onset Diabetes, Other Vascular Events

Exploratory Endpoints: DVT/PE; SVT; hospitalizations for CHF; PCI/CABG; biomarkers

N = 10,000 Novartis
What About inflammation Inhibition in Acute Coronary Syndromes?

doi:10.1093/eurheartj/ehu272

The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study

Allison C. Morton¹, Alexander M. K. Rothman¹,², John P. Greenwood³, Julian Gunn¹,², Alex Chase⁴, Bernard Clarke⁵, Alistair S. Hall³, Keith Fox⁶, Claire Foley⁷, Winston Banya⁷, Duolao Wang⁸, Marcus D. Flather⁷,⁹, and David C. Crossman¹⁰*
Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Stefan M. Nidorf, MD, MBBS,* John W. Eikelboom, MBBS,† Charley A. Budgeon, BSc (Hons),‡ Peter L. Thompson, MD§

Perth, Australia; and Hamilton, Ontario, Canada

Study Design

Hospitalization w/ Myocardial Infarction (NSTEMI ≤24h from last sx, STEMI ≤12h sx onset)

RANDOMIZE 1:1
DOUBLE BLIND

Losmapimod
BID

PLACEBO

Losmapimod: A potent p38 MAPK Inhibitor

Hypothesis: losmapimod will attenuate inflammatory processes in the vascular wall, stabilizing plaques and reducing risk of subsequent plaque rupture

Study Treatment for 12 weeks

End of Treatment Visit (Primary Efficacy Evaluation)

Post-treatment F/U at 24 weeks

1° EP: CV Death, MI, Severe Recurrent Ischemia → Urgent Revasc
Principal 2° EP: CV Death, MI
We are exceptionally lucky to be in an era with ongoing direct tests of both the LDL hypothesis and the inflammation hypothesis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Event Reduction?</th>
<th>LDL-Lowering?</th>
<th>CRP-Lowering?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ezetimibe + Statin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>??</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Alirocumab</td>
<td>??</td>
<td>Yes</td>
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<tr>
<td>Bococizumab</td>
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<td>Yes</td>
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<tr>
<td>Canakinumab</td>
<td>??</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Low Dose MTX</td>
<td>??</td>
<td>No</td>
<td>Yes</td>
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</tbody>
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