Cardiology and vascular medicine 2012

Management of vascular inflammation in ACS

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Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome (n=7392)

(Hazard ratio, 2.59 (95% CI, 1.50–4.46); P=0.001)

(UPRAISE-2, NEJM 2011)
High Telomerase Activity in Neutrophils from Unstable Coronary Plaques

Immunostaining of coronary plaque PMN with MPO-7 antibodies

Cell extracts derived from PMN isolated from arterial (A) or venous blood (V) or directly from angioplasty balloon (AB) were assayed for telomerase activity.

< 40 hrs between last episode of angina and sampling

(Narducci et al, JACC 2008)
Activation of innate immunity in acute coronary syndromes (n=18)

(TLR-4)

A  TLR-4 on Monocytes

mean fluorescence activity

0  50  100  150

Thrombus  Peripheral blood  Controls

ACS

P = 0.0061

P < 0.0001

C  TLR-4 on Granulocytes

mean fluorescence activity

0  20  40  60  80

Thrombus  Peripheral blood  Controls

ACS

P = 0.51

P = 0.0008

(Wyss et al, EHJ 2010)
Perturbation of T cell balance in ACS

Altered status of CD4+CD25+ regulatory T cells in ACS (Mor et al, EHJ 2006)

The opposite-direction modulation of CD4+CD25+ Tregs and Th1 cells in ACS (Han et al, Clinical Immunology 2007)

The Th17/Treg imbalance in patients with ACS (Cheng et al, Clinical Immunology 2008)
Cluster analysis according to T cell subsets and their ratio

Cluster analysis

CD4+CD28null T-cells > 4%

Tregs < 5%

Ratio > 2

(Liuzzo et al, submitted)
CRP levels at the very onset of first STEMI (n=1099)

(Cianflone et al, JACC 2011)
Mechanical triggers of plaque fissure: cholesterol crystals

Factors affecting cholesterol crystallization:
- Cholesterol saturation
- Hydration
- Temperature
- pH

(Abela et al, Clin Cardiol 2005, AJC 2009)
Outcome of patients with NSTE-ACS and normal coronary arteries or mild CAD enrolled in TIMI 11B, TIMI 16 and TIMI 22 (9.1% of 7,656 patients)

(Bugiardini et al, Arch Intern Med 2006)
A LAD

B Spasm

A LAD

B LAD

A LCX

B LCX
Tako-Tsubo: role of coronary microvascular dysfunction

Perfusion defect at baseline

Transient improvement during ADN

(Galiuto et al, EHJ 2010)
Pathogenesis of acute coronary syndromes

Non obstructive ATS

Proximal or distal spasm

Smooth muscle cell hyperreactivity

Vasoconstrictor stimuli

Auto-antigens

Obstructive ATS and systemic inflammation

Infectious agents

Plaque erosion or fissure

White/red thrombus

Plaque fissure

Obstructive ATS without systemic inflammation

Systemic stress

Local stress
SCA

Obstructive ATS without systemic inflammation

Prevention of mechanical plaque rupture

Obstructive ATS with systemic inflammation

Anti-inflammatory therapy

Non obstructive ATS

Specific vasodilators
How to target inflammation in ACS?

- **DMARDs**
  - Methotrexate

- **Key cytokine blockers**
  - IL-1β blockers

- **T cell modulators**
  - Statins

- **Antibiotics Vaccines**
  - Influenza vaccination
### Low dose methotrexate 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 Choi 2002</td>
<td>RA</td>
<td>0.4 (0.2–0.8)</td>
<td>Total mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></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⁻¹</td>
</tr>
<tr>
<td>Netherlands van Helm 2006</td>
<td>RA</td>
<td>0.3 (0.1–0.7)</td>
<td>CVD</td>
<td>LDM only</td>
</tr>
<tr>
<td></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 Pradanovich 2005</td>
<td>Psoriasis</td>
<td>0.7 (0.6–0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>0.5 (0.3–0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg wk⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.8 (0.7–1.0)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
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<td></td>
<td>0.6 (0.5–0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg wk⁻¹</td>
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<td>CORRONA Solomon 2006</td>
<td>RA</td>
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<td>CVD</td>
<td>LDM</td>
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<tr>
<td></td>
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<td>0.4 (0.2–0.8)</td>
<td>CVD</td>
<td>TNF-inhibitor</td>
</tr>
<tr>
<td>QUEST-RA Narango 2008</td>
<td>RA</td>
<td>0.85 (0.8–0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></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>
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<td>UK Norfolk 2008</td>
<td>RA, PSA</td>
<td>0.6 (0.4–1.0)</td>
<td>Total mortality</td>
<td>LDM</td>
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<td></td>
<td></td>
<td>0.5 (0.3–1.1)</td>
<td>CV mortality</td>
<td>LDM</td>
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Cardiovascular inflammation reduction trial (CIRT)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent elevation of hsCRP (> 2 mg L\(^{-1}\))

Open label active run-in
LDM 10 mg wk\(^{-1}\)

Randomized
VLDM 10 mg wk\(^{-1}\) + folate

Randomized
Placebo mg wk\(^{-1}\) + folate

Non-fatal MI, non-fatal stroke, cardiovascular death

(Ridker et al., J Throm Haemost 2009)
How to target inflammation in ACS?

DMARDs
- Methotrexate

Key cytokine blockers
- IL-1β blockers

T cell modulators
- Statins

Antibiotics Vaccines
- Influenza vaccination
IL-1β activation

1. PRIMING step
   - NFkB
   - DNA

2. ACTIVATION step
   - Extracellular noxae
   - ROS
   - Phagocytosis
   - Potassium efflux
   - P2X7
   - NLRP3
   - ASC
   - pro-caspase-1
   - Caspase-1
   - Pro-IL-1β
   - Bioactive IL-1β

De novo transcription of inflammasome activating components and pro-1L-1β
IL-1R blockade with anakinra prevents adverse cardiac remodeling after STEMI (n=10)
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

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 CFH; PCI/CABG; biomarkers

(Ridker et al., Am Heart J 2011)
### How to target inflammation in ACS?

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs/Therapies</th>
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<tbody>
<tr>
<td>DMARDs</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Key cytokine blockers</td>
<td>TNF(\alpha) or IL-1(\beta) blockers</td>
</tr>
<tr>
<td>T cell modulators</td>
<td>Statins</td>
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<td>Antibiotics Vaccines</td>
<td>Influenza vaccination</td>
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In vitro effects of atorvastatin on CD4+CD28null and on CD25+ T cells

(Campioni et al, submitted)
# How to target inflammation in ACS?

<table>
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<tr>
<th>Category</th>
<th>Methodologies</th>
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<td>DMARDs</td>
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Influenza vaccination reduces cardiovascular events in patients with ACS (n=439)

(Phrommintikul et al, EHJ 2011)
Anti-inflammatory treatment of ACS

• Innate immunity: ongoing CRT of methotrexate and of IL-1 blockers in ACS are testing this therapeutic target

• Adaptive immunity: T cell repertoire perturbation is a potential new target which needs to be tested in CRT

• Triggers: the promising results with influenza vaccination suggests that reduction of infectious burden is another potential new target
Ox-LDL in atherectomy specimens from stable and unstable plaques

Stable Angina

Unstable angina

(Niccoli et al, J Cardiovasc Med 2007)
ACES: Primary Endpoint Rate

(Grayston et al, NRJM 2005)
Anti-inflammatory Treatment of Acute Coronary Syndromes

R. Della Bona, G. Liuzzo, D. Pedicino, and F. Crea*

Institute of Cardiology, Catholic University, Rome, Italy

Abstract: The past decade has seen a steady growth in the treatment options available for Acute Coronary Syndromes (ACS), as a consequence of our better understanding of ACS pathophysiology. Administration of fibrinolytics in ST-elevation myocardial infarction, and of potent antiplatelet and anticoagulant drugs in all ACS, has allowed us to considerably improve their outcome. Yet, the rate of adverse cardiac events at early follow-up ranges from 15% to 20%. Thus, to further improve the outcome of ACS or to prevent their occurrence, it is important to identify new therapeutic targets.

A number of experimental and clinical studies have highlighted the key role of inflammation in all phases of atherosclerosis, from fatty streaks to disrupted plaques and raised levels of inflammatory markers have been associated to a poor outcome despite optimal treatment, including myocardial revascularization. In this review, we will focus on inflammation as a possible new therapeutic target of ACS, discussing the anti-inflammatory treatments in four sections: 1) non specific anti-inflammatory drugs; 2) specific antagonists of key cytokines; 3) T-cell modulation; 4) immunization as promising therapeutic modality against atherosclerosis.

Keywords: Acute Coronary Syndrome, Inflammation, Methotrexate, Glucocorticoids, Statins, NSAIDs, COX, Key cytokines antagonists, TNF, IL-1, T-cells.
Cholesterol crystal activation of inflammasome

NLRP3
ASC
Caspase-1
Pro-IL1β
IL1β
Kefllux
Cathepsin D

(Rajamaki et al, PLoS 2010)
Activation of innate immunity

(Wyss et al, EHJ 2010)
**COX-2 inhibition and risk of CV events: meta-analysis of randomised trials**

(Kearney et al, BMJ 2006)
Mechanisms of anti-inflammatory action of statins

Acetyl-CoA → HMG-CoA → Mevalonate → Isopentenyl-PP

Statins

HMG-CoA Reductase

Liver cell

Geranyl-PP → Farnesyl-PP

Geranylgeranyl-PP

Squalene

CHOLESTEROL

GERANYLGERANYLATED PROTEINS

e.g. Rho, Rac, Rap
Cholesterol crystal activation of inflammasome

- NLRP3
- ASC
- Caspase-1
- Pro-IL1β
- IL1β
- K eflux
- Cathepsin D
Activation of adaptive immunity

Th0

- INF-γ
  Liuzzo et al, Circ 1999

- IL-4
  Eid et al, Circulation 2009

Th1

- IL-17
  Brunetti et al, Coronary Artery Dis 2008

Th2
Targeted Anticytokine Therapy in Patients With Chronic Heart Failure (n=1675)

(Mann et al, Circulation 2004)
IL-1β activation and blockers
Expansion of Human T reg From Patients With T1DM

(Putnam et al, Diabetes 2009)
In RA utilization of DMARDs is associated to a lower CV risk (n=4363)

<table>
<thead>
<tr>
<th></th>
<th>CV all types</th>
<th>Myocardial infarction</th>
<th>Stroke</th>
</tr>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>0.85 (0.81–0.89)</td>
<td>0.82 (0.74–0.91)</td>
<td>0.89 (0.82–0.98)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>0.95 (0.92–0.98)</td>
<td>0.96 (0.91–1.00)</td>
<td>0.98 (0.93–1.03)</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>0.98 (0.94–1.02)</td>
<td>0.94 (0.85–1.03)</td>
<td>0.87 (0.76–1.01)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>0.92 (0.87–0.98)</td>
<td>0.82 (0.69–0.98)</td>
<td>0.90 (0.79–1.03)</td>
</tr>
<tr>
<td>Gold</td>
<td>0.99 (0.95–1.03)</td>
<td>1.04 (0.98–1.10)</td>
<td>0.98 (0.89–1.07)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>0.59 (0.43–0.79)</td>
<td>0.52 (0.26–1.06)</td>
<td>0.91 (0.65–1.28)</td>
</tr>
</tbody>
</table>

(Naranjo et al, Arthritis Research & Therapy 2008)
Cholesterol crystal by micro-OCT

(Liu et al, Nature Med 2011)