Is there any role of inflammation in acute coronary syndromes?

Robert J. Gil, MD, PhD, FESC

1- Invasive Cardiology Dept., Centre of Postgraduate Medical Education
2- Mossakowski Medical Research Centre, Polish Academy of Sciences,
   Central Hospital of the Internal Affairs Ministry, Warsaw, Poland
Progression of atherosclerosis in the coronary arteries – „simplified version”.

Adapted from (Wikimedia Commons, 2007)
Compensatory enlargement of human atherosclerotic coronary arteries


Luminal area is not endangered until more than 40% of IEL is destructed and occupied by plaque.

Coronary artery disease is a disease of arterial wall disease not lumen.
Normal Coronary Vessel 2019

High resolution imaging allows clear delineation of healthy vessel layers

Plaque Types in OCT - Recognition

<table>
<thead>
<tr>
<th></th>
<th>Bright</th>
<th>Deep penetration depth</th>
<th>Homogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous</td>
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<td>Lipid</td>
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<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td>Heterogeneous</td>
</tr>
</tbody>
</table>

- **Fibrous**
  - Bright
  - Deep penetration depth
  - Homogeneous

- **Lipid**
  - Dark
  - Diffuse edge
  - Low penetration depth
  - Homogeneous

- **Calcium**
  - Dark
  - Sharp edge
  - Deep penetration depth
  - Heterogeneous
Distinct mechanisms may trigger coronary thrombosis due to superficial erosion vs. fibrous cap rupture.

Coronary Artery Cross Sections

- Lumen
- Thin fibrous cap
- Intima
- Media
- Tissue Factor+ macrophages
- Collagen-rich intima
- PMN + NETs
- Internal Elastica
- External Elastica

**Thrombosis due to Erosion**
- Fibrous cap thick & intact
- “White” platelet-rich thrombus
- Collagen trigger
- Smooth muscle cells prominent
- Often sessile, non-occlusive Thrombus
- Usually less remodelled outward
- Neutrophil extracellular traps (NETs) involved
- More frequent in Non-STEMI?

**Thrombosis due to Rupture**
- Thin fibrous cap with fissure
- “Red” fibrin-rich thrombus
- Tissue Factor trigger
- Macrophages prominent
- Often occlusive thrombus
- Usually expansively remodelled
- Less NET involvement?
- More frequently cause STEMI?
OCT in ACS

Red thrombus
Plaque rupture
Plaque rupture

White thrombus
Plaque erosion
Plaque thrombi
Endothelium: role in atherosclerosis progression

Normal endothelium

Diseased endothelium

Hyperlipidemia
Hypertension
Diabetes
Turbulent blood flow
Atherosclerosis development
Inside atherosclerotic vessel wall – multidirectional processes
Collagen synthesis and breakdown in the maintenance of the fibrous cap integrity
Biological processes central to the pathogenesis of atherosclerosis.
The role of immunometabolism in atherosclerosis
Atherosclerosis: from plaque initiation, inflammation and progression to macrocalcification

Different Types of Vulnerable Plaques

Major underlying cause of ACS
Is there any role of inflammation in ACS?

YES! Its role is huge!

Can we use this fact in the fight against atherosclerosis?
Critical Role of the IL-1β to IL-6 to CRP Pathway in Atherothrombosis

- Cholesterol Crystals
- Neutrophil Extracellular Traps
- Atheroprene Flow
- Hypoxia

Pro-IL-1β
Caspase-1
Active IL-1β
NLRP3 Inflammasome

IL-1β
IL-6
PAI-1
Fibrinogen
Liver

Vascular Inflammation
Endothelial Dysfunction
Atherosclerosis

hsCRP
Risk
High ........................................ >3
Intermediate ......................... 1-3
Low .................................. <1

Mechanisms and potential targets of inflammation in atherosclerosis.
Mechanisms and potential targets of inflammation in atherosclerosis.
Key binding sites of Colchicine and their effects.

“Reducing the level of inflammatory cytokines such as tumor necrosis factor alpha (TNF-a) and interleukin (IL)-6 by suppressing the activation of the caspase-1 which convert pro-IL to active IL.”
The Beneficial Therapy with Colchicine for Atherosclerosis via Anti-inflammation and Decrease in Hypertriglyceridemia.

Spartalis M1,2, Spartalis E3, Tzatzaki E1, Tsilimigas DI3, Moris D4, Kontogiannis C5, Kaminiotis VV3, Paschou SA6, Chatzidou S5, Siasos G7, Voudris V1, Ilipopoulos DC3.

Author information
1 Division of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece.
2 ESC Working Group on Thrombosis, Sophia Antipolis Cedex 06903, France.
3 Laboratory of Experimental Surgery and Surgical Research, University of Athens, Medical School, Athens, Greece.

CONCLUSION: Colchicine reduces the levels of inflammatory markers, stabilizes the coronary plaque, leads to more favorable cardiac healing after damage, and reduces the acute coronary syndromes event recurrence. Colchicine reduces the myocardial infarct size, myocardial fibrosis, and improves the hemodynamic parameters. Several studies report the potential attenuating role of colchicine on triglyceride levels. Current evidence though regarding the pathophysiological mechanism of colchicine's triglyceride-lowering effect remains scarce.

OBJECTIVE: This review aims to give a conceptual description of the potential therapeutic benefits and effects of colchicine in inflammation-mediated atherosclerotic disease and hypertriglyceridemia.

METHOD: A complete literature survey was performed using the PubMed database search to collect available information regarding colchicine, atherosclerosis, and hypertriglyceridemia.

RESULTS: A total of 42 studies met the selection criteria for inclusion in the review. Inflammation is a well-known key mediator of atherogenesis in coronary artery disease. Colchicine has direct anti-inflammatory effects by inhibiting critical inflammatory signaling networks as the inflammasome, pro-inflammatory cytokines, and expression of adhesion molecules, preventing both local chemoattraction of inflammatory cells such as neutrophils and systemic inflammation including the decrease of the release of IL-1β by the neutrophils.

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# Upcoming trials with Colchicine

<table>
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<tr>
<th>Clinical trial number</th>
<th>Study type</th>
<th>Target number</th>
<th>Clinical Setting</th>
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</thead>
<tbody>
<tr>
<td>ACTRN12614000093684</td>
<td></td>
<td>(LoDoCo 2 trial)</td>
<td>Randomized double-blind, placebo control trial</td>
</tr>
<tr>
<td>(COLET trial)</td>
<td>Randomized double-blind, placebo control trial</td>
<td>106</td>
<td>- To assess the effects of colchicine on vascular inflammation measured by metabolic imaging and plasma biomarkers in patients with atherosclerotic vascular disease.</td>
</tr>
<tr>
<td><strong>NCT01906749</strong></td>
<td></td>
<td>(COACS trial)</td>
<td>Multicenter, Randomized double-blind, placebo control trial</td>
</tr>
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<td><strong>500</strong></td>
<td>- To assess the effect of low-dose colchicine (0.5mg/day) on overall mortality, new coronary syndromes, and ischemic stroke at 2 years after an acute coronary syndrome.</td>
<td>NCT01709981</td>
<td>Randomized double-blind, placebo control trial</td>
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<tr>
<td><strong>400</strong></td>
<td></td>
<td>- To characterize a potential mechanism of benefit in patients</td>
<td>- To determine the effects of colchicine on peri-procedural...</td>
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Cardiovascular Inflammation Reduction Trial (CIRT)

Flow Diagram

Stable CAD (past history of MI or multi-vessel CAD on angiogram)
   On Statin, ACE/ARB, BB, ASA

   Persistent Evidence of Inflammation
   Type 2 Diabetes or Metabolic Syndrome

   - To evaluate in a randomized, double-blind, placebo-controlled trial
     whether LD-MTX given at a target dose of 15 to 20 mg po weekly will reduce rates
     of myocardial infarction, stroke, or cardiovascular death among patients with
     stable coronary artery disease and either type 2 diabetes or metabolic
     syndrome.

   LD-MTX 15-20 mg po once weekly + daily folate 1mg
   LD-MTX placebo po once weekly + daily folate 1mg

   MACE, MACE+, Cardiovascular Death

417 US and Canadian Sites
4786 Patients Randomized
10 Patients Lost to Follow-Up
Cardiovascular Inflammation Reduction Trial (CIRT)
Primary Result: Major Adverse Cardiovascular Events (MACE)

Hazard ratio, 1.01 (95% CI, 0.82-1.25), P=0.91

MACE
N (Incidence Rate Per 100 person years)
170 (3.46) LD-MTX
167 (3.43) Placebo

Cardiovascular Inflammation Reduction Trial (CIRT)
Primary Result: MACE+ – Plus Hospitalization for UA Requiring Urgent Revascularization (MACE+)

Hazard ratio, 0.96 (95% CI, 0.79-1.16, P=0.67)

MACE+
N (Incidence Rate Per 100 person years)
201 (4.13) LD-MTX
207 (4.31) Placebo

No. at risk:
Low-Dose Methotrexate
Placebo

Low-Dose Methotrexate
Placebo

No. at risk:
Low-Dose Methotrexate
Placebo

0.00
0.05
0.10
0.15
Cumulative Incidence

No. at risk:
Low-Dose Methotrexate
Placebo

0
1
2
3
4
Follow-up (years)
CANTOS: Study design

Inclusion criteria: Stable patients with a history of MI on SOC therapies and hs-CRP ≥ 2 mg/L (N=10,061)

- Canakinumab 50 mg SC once every 3 months N=2,170
- Canakinumab 150 mg SC once every 3 months N=2,284
- Canakinumab 300 mg SC once every 3 months N=2,263
- Placebo N=3,344

Median follow-up: 3.7 years

Primary endpoint: composite of non-fatal MI, non-fatal stroke, and CV death

Canakinumab is a fully human monoclonal antibody that reduces plasma levels of interleukin-6 and high-sensitivity C-reactive protein, without lowering LDL-c. It has been approved for clinical use in rheumatologic disorders.

MI: myocardial infarction; hs-CRP: high sensitivity C-reactive protein; SC: subcutaneous; CV: cardiovascular; SOC: standard of care

Ridker PM, et al. NEJM 2017; Ridker PM, et al. The Lancet 2017
Figure 3

Cumulative incidence and hazard ratios of cardiovascular mortality (Left) and all-cause mortality (Right) among CANTOS participants allocated to either placebo or canakinumab according to whether post-randomization on-treatment hsCRP levels were above or below 2 mg/L. Hazard ratios are adjusted for age, sex, smoking status, hypertension, diabetes, body mass index, baseline concentration of hsCRP, and baseline concentration of LDL-C. HR, hazard ratio; CI, confidence interval. Ridker (37).
Conclusion

Inflammation plays an essential role in the pathophysiology of atherosclerotic plaque formation, progression and maintaining of fibrous cap integrity (plaque protection for: erosion, fissuring, rupture), which conclusively causes ACS episodes.

The therapeutic effects of currently available anti-inflammatory agents are not completely satisfactory and require further research.