Inflammatory hypothesis as linked to the biology of atherosclerosis
Vascular Injury

- Activation of inflammatory cells and signals
- Cascade of events (injury – healing) initiates and perpetuates the atherosclerotic process
Inflammatory Reaction

- Plaque instability
- Rupture, fissuring, erosion
- Substrate for thrombogenesis
Inflammatory Markers

- High sensitivity C-reactive Protein
- Interleukin-6
- Increased incidence of cardiovascular events, *independent of cholesterol levels*
Inflammatory Markers

• Statins reduce cholesterol levels and inflammatory markers
• Statin efficacy related to both lipid lowering and inhibition of inflammation
Does inhibition of vascular inflammation independently reduce the risk of atherosclerosis?
Inflammatory Markers

• Interleukin - 1β – cytokine central to the inflammatory response

• Cytokine modulates the interleukin-6 signaling pathway
Canakinumab

- Human monoclonal antibody
- Blocks interleukin - 1β
- Antiinflammatory effects
- Reduces high sensitivity C-reactive protein and interleukin - 6 plasma levels
- No effect on LDL
- Can direct antiinflammatory therapy, reduce cardiovascular risk – proof-of-concept
CANTOS Trial

- Stable post MI patients with elevated c-reactive protein (≥ 2 mg/liter)
- Randomized
- Double-blind
- Placebo-controlled
CANTOS Trial

- 10,061 randomized
- 1.5 : 1 : 1 : 1

Subcutaneous injections of **Canakinumab** every 3 months
CANTOS Trial

Primary end points:

- Nonfatal MI
- Nonfatal CVA
- CV death

Secondary end points:

- 1° plus unstable angina leading to urgent revascularization
- Death from any cause
Canakinumab

Reduced levels of high-sensitivity C-reactive protein in dose dependent fashion
Canakinumab

No significant reduction in LDL

LDL Cholesterol Level

Median Cholesterol = 82 mg/dl

Percent change from baseline

MONTHS

50 mg
150 mg
300 mg
Placebo
Canakinumab

- **150 mg** dose lowered incidence of primary endpoint (↓ MI)
- Increased deaths from infection
- Decreased cancer mortality
CANTOS Trial

• First trial to infer clinical cardiovascular benefit by targeting inflammation

• Modest absolute clinical benefit at a cost

• Challenge to find agents with enhanced effect without major infection risk
Atheroprotection

- Multitude of inflammatory pathways
- Challenge – inhibit key inflammatory pathways triggering atherothrombosis without altering immune system
Thank You

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