CANTOS Trial Validates the Inflammatory Pathogenesis of Atherosclerosis

Setting the Stage for a New Chapter in Therapeutic Targeting

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Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.

—Winston Churchill

The CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) provides intriguing support for the inflammatory hypothesis of atherosclerosis and cancer in man, demonstrating diverse clinical benefits of inhibiting IL (interleukin)-1β for cardiovascular events and lung cancer. Limited effects on cardiovascular mortality and safety concerns raised by a higher incidence of fatal infection warrant further studies to identify patient subgroups which profit most from anti-inflammatory therapy and a careful pursuit of alternative targets.

Abundant evidence from experimental and clinical studies has lend strong support to the hypothesis that inflammation contributes to the pathogenesis of atherosclerotic disease in conjunction with or beyond elevated lipid levels; however, ultimate proof by selective anti-inflammatory treatment in a clinical trial remained elusive for decades. This has now changed with the results of the CANTOS, a double-blind trial involving high-risk patients with prior myocardial infarction (MI) and a residual inflammatory response (defined by hsCRP [high-sensitivity C-reactive protein] levels >2 mg/L despite intensive statin therapy), who were randomized to canakinumab (50, 150, or 300 mg every 3 months) or placebo.[1] Canakinumab, a human monoclonal antibody targeting IL-1β as the master cytokine of innate immunity, dose dependently reduced hsCRP and IL-6 levels by ≤43% from baseline. At 150 mg (but not the other doses), canakinumab significantly lowered the risk for the primary (MI, stroke, cardiovascular death) and secondary end points (hazard ratio [HR], 0.85 and 0.83, respectively). Adversely, canakinumab was associated with leukopenia and a higher incidence of fatal infection. Whereas no significant difference in all-cause or cardiovascular mortality was observed, canakinumab strikingly reduced cancer mortality (exploratory results indicating HR 0.23, for lung cancer), supporting a role of inflammation in cancer progression.[2] Here, we aim to contemplate in how far CANTOS merits praise as in the J.S. Bach-Cantata *rejoice, you hearts*.

Inflammation is vital. Without its innate and adaptive immune responses featuring a central role of IL-1β, we would be defenseless against microbial pathogens, toxic or sterile damage. As our lifespan has been prolonged much beyond the reproductive age, we increasingly experience this highly evolved defense system causing chronic inflammation. As 1 paradigm, atherosclerosis occurs when cholesterol deposits or crystals are not sufficiently removed and inflammatory cells accumulate in the arterial wall, driving plaque progression, erosion and rupture leading to stroke and MI. Since the Framingham studies, metabolism and inflammation have merged as the main risk factors determining this pathogenesis. The prognostic success of improving glycemic control and lipid lowering confirmed the relevance of metabolism, leading to affordable and well-tolerated medications. Notably, biomarkers of inflammation such as hsCRP and IL-6 have been associated with increased risk of cardiovascular events independent of cholesterol levels.[3] Moreover, beneficial outcomes after statin therapy could be related to a reduction in both cholesterol levels and inflammation markers, for example, in the JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin).[4] In contrast, anti-inflammatory therapies such as corticosteroids or nonsteroidal anti-inflammatory drugs display atherogenic side effects or increase cardiovascular events.[5] Despite a growing body of experimental studies,[6] clinical evidence that controlling vascular inflammation independently of lipid lowering limits cardiovascular risk has not been provided. Hence, a causative inflammatory pathogenesis of atherosclerosis has not been elucidated let alone unequivocally proven.

The CANTOS trial enrolling 10061 high-risk patients defined by prior MI and persistent inflammation has now resolved this long-standing enigma, validating the hypothesis of a relevant and lipid-independent inflammatory pathogenesis of atherosclerosis with its breakthrough findings. At 150 mg, canakinumab met prespecified multiplicity-adjusted statistical significance thresholds for the primary end point (HR, 0.85; 95% confidence interval [CI], 0.74–0.98; *P*=0.021), mainly lowering rates of MI, and for the secondary end point (HR, 0.83; 95% CI, 0.73–0.95; *P*=0.005) including urgent revascularization for unstable angina during a median 3.7-year follow-up. The proof of concept for a clinically meaningful inflammatory pathogenesis can be deduced from the combination of unchanged LDL (low-densitiy lipoprotein) cholesterol levels, reduced inflammatory markers and the lower rate

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See the Online Data Supplement for the first-page footnotes.

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of cardiovascular events. With a median near 80 mg/dL, LDL cholesterol levels were close to guideline recommendations, albeit these might be further lowered in the PCSK9 era. Whereas anakinra inhibiting IL-1 receptors was found to raise cholesterol levels, it was predictable from previous studies[7] that LDL cholesterol levels would be unaffected, corroborating a selective anti-inflammatory effect. However, other relevant parameters, namely glycemic control (HbA1c) or blood pressure, were not reported. Hence, interference with these risk factors may have occurred. Although the number of patients needed to treat to prevent 1 MI was low (57) at 150 mg, the fact that only this dose achieved a borderline significant reduction in end points may limit enthusiasm, as to expecting a rapid approval for secondary prevention.

Conundrum of Cardiovascular Mortality

It seems counterintuitive that all-cause mortality and particularly cardiovascular mortality were not significantly affected, leaving room for speculation on statistical power. Indeed, death was not a prespecified outcome, and the size of the cohort may have been underpowered after diminishing the intended study population (from 17 200 patients) because of budget issues. Besides MI, the definition of cardiovascular death also included sudden unwitnessed death, death because of chronic heart failure, and stroke-related death. As stroke was not reduced by canakinumab, this may have diluted effects on cardiovascular death. Notably, the original study design was complemented by a 50-mg arm on behalf of the Food and Drug Administration, and just this dose exhibited the largest albeit not significant effect on cardiovascular mortality (HR, 0.80; 95% CI, 0.62–1.03; P=0.083). It is striking that the most significantly reduced event rates at 150 mg were observed for MI (HR, 0.76) and any revascularization (HR, 0.68), whereas confirmed cardiovascular death was not significantly reduced (HR, 0.88). An explanation for the low cardiovascular mortality could be that non–ST-segment–elevation MI (NSTEMI predominated over STEMI). However, the distribution of NSTEMI versus STEMI was not reported. Optimally treated patients (as in CANTOS) have been suggested to carry a higher risk for plaque erosion than for rupture,[6] a notion reflected by a particular benefit in patients with unstable angina and urgent revascularization, which more likely corresponds to NSTEMI.

Albeit the study was not powered to detect such differences, the effect on cardiovascular mortality seemed even less impressive at 300 mg (HR, 0.93). It is tempting to speculate whether adverse effects leading to more complications at higher doses may offset benefits on mortality presumed on the basis of reduced MI and revascularization. A dual role of IL-1β and inflammation after MI may not only contribute to atherothrombosis but also to remodeling, thus affecting cardiovascular death from other causes. Such underlying pathologies were not differentiated and may comprise ventricular arrhythmia, impaired systolic left ventricular function, heart failure, or myocardial scar instability entailing cardiac rupture. Thus, many details and aspects remain incompletely understood. An additional reduction of 15% of cardiovascular events in optimally treated patients is undoubtedly a major success achieved by CANTOS, which places the value of this study beyond a mere proof of principle but warrants a meticulous follow-up analysis.

In this context, it will certainly be important to extend the trial to a more refined study of appropriately selected patient subgroups. Apparently, the reduction in inflammation as monitored by hsCRP was heterogeneous so that differential degrees of responsiveness to canakinumab could be distinguished. The above average responders at 150 mg (as defined by hsCRP reduction greater than the median) experienced a more pronounced reduction for the primary end point (HR, 0.73; Ridker et al, unpublished data), implying that inflammatory pathways affecting atherogenesis and the degree of susceptibility to anti-inflammatory intervention are variable. It would clearly be desirable to identify responders a priori, which may be feasible by including auxiliary biomarkers such as IL-1β or IL-6 in the response-to-treatment stratification. This may include an identification of other patient subgroups which benefit from therapy or which are prone to adverse effects and should be excluded; however, such a hypothesis-generating exercise requires validation in further clinical trials.

Spectrum of Adverse and Unanticipated Effects

On the basis of the anti-inflammatory potency of canakinumab, it had to be expected that benefits would come at the price of serious adverse events of infection. Despite a careful preselection of study participants excluding patients at risk for infectious complications, canakinumab significantly increased the incidence of neutropenia, cellulitis, pseudomembranous colitis, fatal infection, or sepsis across doses. Whereas 0.69% of patients in the placebo group died from infections, 1.16% of patients died in the pooled canakinumab group. Although the type of fatal infections was not detailed, pneumonia and urinary tract infections were not more frequent, indicating a differential role of IL-1β within the multiplicity of bacterial infections. Conversely, favorable effects were encountered, as canakinumab reduced the incidence of arthritis.

The exploratory results reported for cancer mortality, in particular lung cancer, are perhaps among the most fascinating observations in CANTOS. Canakinumab dose dependently decreased the rate of fatal cancer (HR, 0.49 at 300 mg), whereas the incidence of any cancer did not differ, prompting a subgroup analysis.[1,2] Given that smoking is a common risk factor for atherosclerosis and lung cancer and 71% of patients were current or past smokers, lung cancer comprised a large fraction of cancers. Strikingly, both lung cancer mortality and incidence (HR, 0.23 and 0.33 at 300 mg, respectively) were reduced by canakinumab, whereas mortality but not incidence was significantly influenced for nonlung cancer.[2] Preferential effects on lung cancer might be ascribed to the notion that many epithelial cancers have been associated with chronic inflammation, and smoking can cause pulmonary inflammation. Indeed, patients with increased baseline levels of hsCRP and IL-6 were more likely to be diagnosed with lung cancer. It will be interesting to scrutinize whether these observations are restricted to patients with preexisting atherosclerosis, smokers, and anti-inflammatory responders. The unforeseen effect on lung cancer (not being a prespecified end point) awaits validation in future clinical trials.

Road Ahead

Given that canakinumab is expensive (≈$16 000 per infusion), the cost of long-term treatment in patients with chronic inflammation needs to be taken into account. Moreover, the increased incidence of fatal infection raises serious concerns. Those who

died from infection tended to be older and afflicted by diabetes mellitus, defining potential limitations for using canakinumab. Expanding horizons, these caveats should prompt a quest for therapeutic alternatives, which may encompass less specifically targeted approaches. Additional information will become available from the CIRT trial (Cardiovascular Inflammation Reduction Trial) evaluating methotrexate, an inexpensive and proven anti-inflammatory drug, in a similar population. Yet, the choice of IL-1β as a specific therapeutic target for the secondary prevention of atherosclerotic events was not serendipitous. The production of IL-1β is activated by the NLRP3 (NOD-like receptor protein 3) inflammasome, which has been implicated as a metabolic sensor and central relay in atherogenesis triggered by stimuli such as cholesterol crystals, NETs (neutrophil extracellular traps), or disturbed flow (Online Figure I).[6,8,9] Hence, it might be feasible to test less selective strategies directly targeting NLRP3 by small molecule inhibitors (MCC950) or its upstream stimulators, for example, using cyclodextrin to dissolve cholesterol crystals.[10,11] Conversely, IL-1β evokes downstream signaling by IL-6, which was also reduced by canakinumab.

Somatic mutations in the epigenetic regulator TET2 occurring in expanded blood cell clones during aging increase cardiovascular risk and atherosclerotic burden in human carriers, whereas TET2 deficiency in mouse bone marrow is associated with clonal hematopoiesis and accelerated atherogenesis.[10,12] Beyond clonal expansion, TET2-deficient macrophages displayed an increased NLRP3-mediated IL-1β release, explaining higher atheroprotective activity of MCC950 in TET2-deficient chimeras,[10] and an upregulated secretion of the CXC chemokines CXCL1/2/3 and CXCL4.[12] Moreover, the expression of specific inflammasome gene modules affecting IL-1β, CXCL1, and CXCL12 has been associated with death from any cause, hypertension and higher arterial stiffness in elderly patients.[13] These findings may prompt considerations toward exploiting alternative inflammatory targets. Remarkably, CXC chemokines such as CXCL1 and CXCL4 forming synergistic heterodimers with CC chemokines have been implicated in promoting monocyte recruitment and atherosclerosis in mice.[6,14] In turn, peptides targeting heteromeric interactions of CXCL4 and CXCL12 have been identified as novel therapeutic candidates conferring atheroprotection and limiting monocyte recruitment or platelet activation without notable side effects (eg, on clearing infections) in mice.[6,14] Deficiency of ACKR1 (atypical chemokine receptor 1), which binds inflammatory CC and CXC chemokines to regulate their availability, in erythroid cells profoundly changed hematopoiesis in mice, giving rise to a distinct hyper-armed neutrophil phenotype correspondingly observed in Duffy-negative individuals of African ancestry carrying an ACKR1 gene variant.[15] Given the role of neutrophils in atherosclerosis,[9] this may extend the implications of altered hematopoiesis beyond aging to different ethnic backgrounds.[15]

In synopsis, CANTOS provides intriguing support for the inflammatory hypothesis of atherosclerosis and cancer in man, demonstrating diverse clinical benefits of anti-inflammatory therapy. Beyond ramifications for deliberating more specific versus broader anti-inflammatory targets, the ground-breaking results of CANTOS could prompt a more permissive attitude toward treating inflammation in cardiovascular disease. To address safety concerns, this warrants a better identification of patient subgroups benefiting from anti-inflammatory therapy, for example, with concomitant chronic inflammatory diseases or a primarily inflammatory pathogenesis, as well as a better exclusion of patients at risk for serious infections. Overall, CANTOS represents a widely heralded milestone toward fathoming the inflammatory pathogenesis and anti-inflammatory treatment options for atherosclerosis.

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Disclosures

None.

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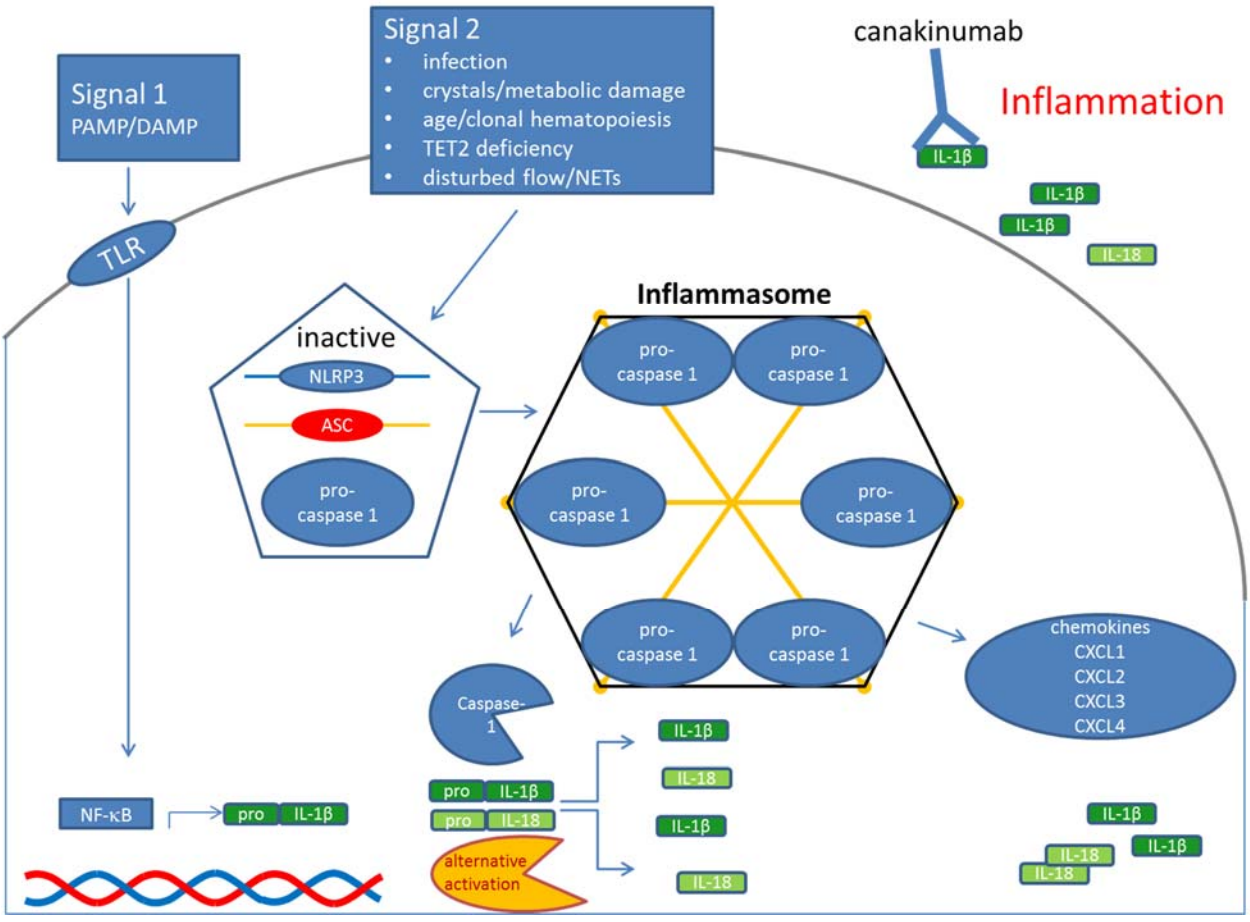

Online Figure. A model of IL (interleukin)-1β–related inflammation. Proinflammatory signaling elicited by damage- or pathogen-associated molecular pattern (DAMP/PAMP) mediators leads to NF-κB (nuclear factor-κB)–dependent transcription of inactive IL-1β and IL- 18 precursors. Additional signals, for example, cholesterol crystals or age-related mutations in epigenetic modifiers, activate the inflammasome by assembling its components (NLRP3 [NOD-like receptor protein 3], ASC, procaspase-1). This results in cleavage of procaspase-1 into mature caspase-1 producing IL-1β/IL-18 and increased chemokine secretion. Alternatively, caspase-independent IL-1 activation can occur. Canakinumab inhibits IL-1β and the inflammatory cascade driving atherosclerosis.

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