

## REVIEW

### Is Atherosclerosis Amenable to Anti-Inflammatory Compounds?

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#### Abstract

The hypothesis of an inflammatory component in the pathogenesis of atherosclerosis has been under investigation for a long time but the data have not been conclusive. No clinical trial of anti-inflammatory, anti-oxidant, or anti-bacterial agents has ever proven efficacious. However, the recent announcement and publication of the CANTOS trial has raised expectations. This pivotal trial showed for the first time that anti-inflammatory therapy targeting the interleukin-1 $\beta$  innate immunity pathway with subcutaneous injections of canakinumab every 3 months conferred significantly, albeit modestly (15%), lower rate of the composite end-point of nonfatal MI, nonfatal stroke and cardiovascular (CV) death than placebo, independent of lipid-level lowering, in patients with prior myocardial infarction (MI). An unexpected corollary of this investigation revealed significant concomitant reduction in lung cancer mortality. Despite the initial enthusiasm about the trial results, sceptics point to that fact that CV mortality was not affected, while the incidence of fatal infections was much higher with the drug compared with placebo, and the cost of this therapy remains currently prohibitive for wider use. Ongoing and future trials with similar or more convenient and less expensive anti-inflammatory agents may provide more data whether such results are reproducible and/or supportive or evidential of the inflammatory hypothesis of atherosclerosis. *Rhythmos 2017; 12(4):63-68.*

**Key Words:** atherosclerosis; coronary thrombosis; inflammation; myocardial infarction

**Abbreviations:** ACS = acute coronary syndrome; CAD = coronary artery disease; CRP = C-reactive protein; CV = cardiovascular; IL = interleukins; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial

#### INTRODUCTION

For a long time, investigators have tried to prove that inflammation plays a causative role in atherosclerosis, however, the precise link has remained elusive.<sup>1-4</sup> No clinical trial of anti-inflammatory, anti-oxidant, or anti-bacterial agents had demonstrated efficacy in combating this common disease, i.e. until to date.<sup>5</sup> The recent announcement and publication of the CANTOS trial<sup>6</sup> has stirred some initial enthusiasm but also skepticism.<sup>7</sup>

#### CANTOS Trial

The CANTOS trial was conducted by a team of investigators who had invested on the inflammatory hypothesis of atherosclerosis trying for a long time to prove their case.<sup>3, 6, 8, 9</sup> They randomized 10,061 patients (mean age 61; 90% being treated with statin) with previous myocardial infarction (MI) and a high-sensitivity C-reactive protein level (hsCRP) of  $\geq 2$  mg/l randomized to 3 doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months), a monoclonal antibody targeting interleukin-1 $\beta$ , and placebo.<sup>6</sup> The study was supported by the manufacturer of the antiinflammatory compound (canakinumab, *Ilaris*®, Novartis).

At 48 months, the median reduction from baseline in the hsCRP was 26% greater in the group that received the 50-mg dose of canakinumab, 37% greater in the 150-mg group, and 41% greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median follow-up of 3.7 years, the incidence rate for the primary end point (nonfatal MI, nonfatal stroke, or cardiovascular – CV death) was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group (hazard ratio-HR 0.93;  $p=0.3$ ), 3.86 events per 100 person-years in the 150-mg group (HR 0.85,  $p=0.021$ ), and 3.90 events per 100 person-years in the 300-mg group (HR 0.86,  $p=0.031$ ). The 150-mg dose, but not the other doses, met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (HR vs placebo, 0.83;  $P = 0.005$ ). Canakinumab was associated with a higher incidence of neutropenia, thrombocytopenia and fatal infection and sepsis than was placebo. There was no significant difference in all-cause mortality. The authors concluded that antiinflammatory therapy targeting the interleukin-1 $\beta$  innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent CV events than placebo, independent of lipid-level lowering. Interestingly, cancer, particularly lung cancer, mortality was significantly lower with canakinumab than with placebo. Also, canakinumab resulted in significantly fewer reports of arthritis, gout, and osteoarthritis than did placebo.

In a separate publication, the benefit from canakinumab was shown to be limited in participants who achieved hsCRP concentrations  $< 2$  mg/L who had a 25% reduction in major adverse cardiovascular events (HR=0.75,  $p<0.0001$ ), whereas no significant benefit was observed among those with on-treatment hsCRP concentrations of  $\geq 2$  mg/L (HR=0.90,  $p=0.11$ ).<sup>10</sup>

### **Critique of the CANTOS Trial**

The accompanying editorial in the *New England Journal of Medicine*<sup>7</sup> points to the fact that there was no observed reduction of CV mortality and also to the worrisome increase in fatal infections. Furthermore, the exuberant cost of such therapy is also pointed out as this agent is priced at ~\$200,000 per year in the US given monthly for approved indications (<https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm522283.htm>). These indications comprise rare and serious auto-inflammatory diseases in adult and pediatric patients: periodic fever syndrome called Cryopyrin-Associated Periodic Syndromes (CAPS), active systemic juvenile idiopathic arthritis, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS); Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD); and Familial Mediterranean Fever (FMF). The latter three syndromes are hereditary diseases that are characterized by periodic attacks of fever and inflammation, as well as severe muscle pain. The editorial mentions that an ongoing trial (CIRT)<sup>11</sup> is testing another well-known anti-inflammatory agent, low-dose methotrexate, in patients with diabetes or the metabolic syndrome and a previous MI, and concludes that “the modest absolute clinical benefit of canakinumab cannot justify its routine use in patients with previous MI until we understand more about the efficacy and safety trade-offs and unless a price restructuring and formal cost-effectiveness evaluation supports it”.

In a separate article published in the *Lancet*, the CANTOS authors reported a relative risk reduction of 51% with the 300-mg dose, mostly driven by a 77% reduction in death from lung cancer.<sup>12</sup> Thus, some believe that the company may be promoting the drug more for its efficacy in lung cancer rather than for its CV effects!

Enthusiasm about the use of the drug in cardiology is drastically tempered by the lack of effect of the drug on CV mortality, and also by the significant increase in fatal infection and sepsis, and, of course, by the exuberant cost of such therapy. The modest (15%) decrease in the risk for the composite primary end point of nonfatal MI, nonfatal stroke, and CV death compared with placebo,<sup>6</sup> although statistically significant ( $p=0.02075$ ) and contributing to the inflammatory hypothesis of atherosclerosis, it remains doubtful whether this effect will turn out to be clinically significant. The results of the ongoing CIRT trial with methotrexate are eagerly awaited.<sup>11</sup>

### **Inflammatory Atherosclerotic Process**

Atherosclerosis has been characterized as a chronic inflammatory disease of the arterial vessel wall.<sup>5, 13</sup> Atherosclerotic lesions show features of inflammation

akin to those found in typical inflammatory and auto immune disease such as rheumatoid arthritis.<sup>14</sup> A variety of cells from the vessel wall may participate in this inflammatory response via complex pathways.<sup>15</sup> Endothelial dysfunction has conventionally been considered the initiator of the atherosclerotic process. The migration and proliferation of smooth muscle cells also play a crucial role. In addition, the fibroblasts from the adventitia and adipocytes from perivascular adipose tissue have also been implicated in atherosclerosis. Furthermore, a plethora of cytokines produced by different cells from the arterial vessel wall, including endothelium-derived relaxing factors, endothelium-derived contracting factors, tumor necrosis factors, interleukin, adhesion molecules, interferon, and adventitium-derived relaxing factors, have been considered contributors to the pathogenesis of atherosclerosis.

The inflammatory response in atherosclerosis is regulated by both the innate and adaptive immune system via the action of cytokines, a diverse group of low-molecular weight proteins comprising the interleukins (IL), chemokines, colony-stimulating factors (CSF), tumor necrosis factors (TNF), the interferons (IFN) and transforming growth factors (TGF).<sup>16</sup> Attenuating cytokine-induced inflammation and promoting the actions of anti-inflammatory cytokines represent potential therapeutic targets. The athero-protective effects of statins and certain other agents (e.g. estradiol) may be attributed to their pleiotropic anti-inflammatory properties. More specific anti-inflammatory agents, like canakinumab tested in the CANTOS trial,<sup>6</sup> or methotrexate being tested in the Cardiovascular Inflammation Reduction Trial (CIRT),<sup>11</sup> have already been proven beneficial in the treatment of other inflammatory disorders like rheumatoid arthritis, and other chronic inflammatory diseases. Furthermore, the protective roles of regulatory T cells (Tregs) and cytokines produced by them (IL-10 and TGF- $\beta$ ), as well as microRNAs (miRNA) that may mitigate cytokine-mediated inflammation in atherosclerosis are actively investigated in an attempt to block pro-inflammatory and enhance anti-inflammatory cytokine actions in combating atherosclerosis. In addition to IL-1 $\beta$  targeted in the CANTOS trial, other ILs, like IL-37, also a member of the IL-1 family, have been proposed as promising potential therapeutic targets in preventing or treating atherosclerosis.<sup>17</sup> IL-32 is a new cytokine, possibly contributing to the increased CV risk.<sup>18</sup> A genetic polymorphism in IL-32 has been shown to reduce pro-inflammatory cytokine production and increase HDL cholesterol levels, most likely reducing inflammation and lower the CV risk.

Inflammasomes are an integral part of the innate immunity, and the NLRP3 (nucleotide-binding oligomerization domain [NOD], leucine-rich family [NLR] pyrin domain containing 3) inflammasome, also known as NALP3 (cryopyrin), plays an important role in atherosclerosis.<sup>19-21</sup> Activated cryopyrin, expressed predominantly in macrophages, detects products of damaged cells such as extracellular ATP and crystalline uric acid, and in turn triggers an immune response. Mutations in the NLRP3 gene are associated with a number of organ specific autoimmune diseases. NOD-like receptors (NLRs) can cooperate with Toll-like receptors (TLRs) and regulate inflammatory and apoptotic response.

Inflammasomes are cytosolic protein complexes formed in response to offending proteins and lead to the production of proinflammatory enzymes such as caspase 1, resulting in activation of proinflammatory cytokines such as IL-1 $\beta$  and IL-18 that lead to cellular apoptosis. Although lipid deposition in the plaque has long been considered a consequence of inflammation and cell death, activation of inflammasomes by cholesterol crystals provides evidence that hyperlipidemia actually promotes inflammation by triggering vascular wall inflammatory responses leading to progression of atherosclerosis.<sup>21</sup> The process may be attenuated by dietary modification and statins' pleiotropic effects.

Through suppression of NLRP, compounds, such as resveratrol, a flavonoid that has been shown to reduce inflammation, moderate alcohol intake which has also been proposed to have a cardioprotective effect, and the antidiabetic drugs, dipeptidyl dipeptidase 4 inhibitors, may exert their anti-inflammatory effects. Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors have emerged as new and potent cholesterol-lowering drugs.<sup>22</sup> Clinical studies also suggest that PCSK9 is involved in atherosclerotic inflammation, while animal data indicate that PCSK9 gene interference could suppress atherosclerosis directly through decreasing vascular inflammation.<sup>23</sup>

At least three major components of the inflammasome pathway – NLRP3, caspase 1, and IL-1 $\beta$ , have been suggested as potential therapeutic targets. Cholesterol crystals have been considered to incite inflammation in atherosclerotic plaques by stimulating the caspase-1-activating NLRP3 inflammasome, which results in cleavage and secretion of IL-1 $\beta$  and IL-18 and finally leads to increased production of other inflammatory cytokines.<sup>24</sup> Furthermore, there is evidence that autophagy regulates NLRP3 inflammasome activation and has a atheroprotective role; on the other hand, when autophagy becomes dysfunctional, atherosclerotic plaque progression

occurs.<sup>25</sup> These findings have raised the possibility and guide efforts to develop novel anti-inflammatory strategies for prevention and treatment of atherosclerotic cardiovascular disease.

Canakinumab is an IL-1 $\beta$  blocker. As shown in the CANTOS trial,<sup>6</sup> a major concern with the development and use of anti-inflammatory agents or immune modulators for atherosclerosis relates to increased incidence of infection due to immune suppression; furthermore, another concern relates to increased incidence of malignancy, although in the CANTOS trial, the opposite was observed. Thus, the challenge remains to devise ways to target the immune mechanisms that produce anti-atherosclerotic effects without generalized immune suppression.

Other anti-inflammatory agents have also been employed in CAD patients.<sup>26</sup> In a clinical trial comprising 532 patients with stable CAD randomized to colchicine (0.5 mg/d) on top of aspirin and/or clopidogrel and statins, the primary outcome (incidence of acute ACS, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) occurred in 15 of 282 patients (5.3%) who received colchicine and 40 of 250 patients (16%) assigned no colchicine (hazard ratio: 0.33;  $p < 0.001$ ; number needed to treat: 11).<sup>27</sup> The authors concluded that colchicine (0.5 mg/day) administered in addition to statins and other standard secondary prevention therapies appeared effective for the prevention of CV events in patients with stable CAD.

A phase II RCT randomized 182 patients with NSTEMI-ACS, presenting <48 h from onset of chest pain to subcutaneous IL-1receptor antagonist (IL-1ra) or placebo for 14 days.<sup>28</sup> CRP over the first 7 days was: IL-1ra group, 21.98 mg day/L; placebo group, 43.5 mg day/L (geometric mean ratio = 0.51 mg/L;  $P = 0.0028$ ). In the IL-1ra group, 14-day achieved high-sensitive C-reactive protein ( $P < 0.0001$ ) and IL-6 levels ( $P = 0.02$ ) were lower than Day 1. Sixteen days after discontinuation of treatment (Day 30) high-sensitive C-reactive protein levels had risen again in the IL-1ra group [IL-1ra; 3.50 mg/L (2.65-4.62); placebo; 2.21 mg/L (1.67-2.92),  $P = 0.022$ ]. MACE at Day 30 and 3 months was similar but at 1 year there was a significant excess of events in the IL-1ra group.

Another potential target for anti-inflammatory treatment in atherosclerosis is interleukin-6 (IL-6), an inflammatory cytokine that plays a central role in propagating the downstream inflammatory response leading to atherosclerosis.<sup>29</sup> IL-6 release is stimulated by acute infections, chronic inflammatory conditions, obesity, and physiologic stress. Individuals with a variant in the IL-6 receptor that impairs classic IL-6 signaling were found to have a decreased risk for CAD. Tocilizumab, a

monoclonal antibody that targets the IL-6 receptor and reduces symptoms in patients with rheumatoid arthritis, has been shown to improve endothelial function in a high-risk population, however it increases total cholesterol and LDL levels.<sup>30</sup>

### **Other (Non-Inflammatory) Mechanisms of Acute Coronary Syndromes**

In a recent review of acute coronary syndromes (ACS),<sup>31</sup> seasoned investigators point out that plaque rupture or erosion in ACS may occur not only in presence of inflammation, but also in its absence. Furthermore, ACS may even occur without apparent epicardial coronary artery thrombus or stenosis (e.g. spasm, microvascular disease, etc.). Thus, a more individualized approach might be in order for managing these syndromes, based on diverse pathophysiology and mechanisms, rather than an oversimplified general athero-thrombo-inflammatory strategy. Therefore, for patients with suspected active inflammation (e.g. high hs-CRP), anti-inflammatory agents might be considered; among them colchicine, the fully humanized anti-IL-1 $\beta$  monoclonal antibody, canakinumab, methotrexate, or even vaccines<sup>13</sup> appear promising. For patients with plaque rupture without systemic inflammation, intensive lipid lowering treatment might protect against plaque destabilization, and sympathetic inhibition may avert plaque rupture triggering. In patients with arterial thrombosis caused by superficial erosion, pharmacological (anticoagulant/antiplatelet therapy) rather than interventional treatment may effectively manage ACS. In patients with ACS without plaque thrombus, nonspecific vasodilators such as long-acting nitrates and calcium channel blockers may alleviate ischemia caused by vasospasm. Finally, genome wide association studies in patients with coronary artery disease may unravel certain complexities of human atherosclerosis related to vulnerable plaque that may have therapeutic ramifications.<sup>32</sup>

### **Inflammatory Markers**

With regards to discerning ACS patients with an active role of inflammation, studies have mostly used the determination of CRP and interleukins (ILs). Of course, these markers are nonspecific and other inflammatory diseases should be excluded before one attributes their elevated levels to inflammatory atherosclerosis. Investigational work with use of 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) has indicated that there is a correlation between the intensity of inflammation of atherosclerotic lesions detected by FDG uptake and circulating inflammatory markers; hence, determining circulating markers of inflammation may be

able to identify patients with unstable inflamed atherosclerotic plaques.<sup>33</sup> Clinical studies indicate a good correlation of circulating inflammatory markers with proclivity to develop ischemic events and subsequent prognosis after ACS.<sup>4</sup>

### **Vulnerable Plaque / Vulnerable Patient**

Recently a 67-year-old smoker and hypercholesterolemic patient who presented with crescendo angina and associated inferolateral wall ischemia was submitted to successful percutaneous coronary intervention (PCI) with direct stenting of a critical lesion in the left circumflex coronary artery.<sup>34</sup> However, 2 days later after hospital discharge he sustained new episodes of acute coronary syndrome with associated anterior wall ischemia attributed to activation of borderline lesions in the mid segment of the left anterior descending coronary artery; these were successfully remedied with implantation of two stents. This is an example among many whereby patients with CAD suffer from activation of more than one coronary lesions, which may not necessarily be angiographically critical lesions.<sup>35</sup> This is apparently well explained by the presence of concurrent "active" inflammation of multiple vulnerable plaques which may rupture, a process set in motion by inflammation involved in the thinning of the fibrous cap, thus predisposing the plaque to rupture. The existence of multiple types of vulnerable plaques suggests that atherosclerosis is a diffuse inflammatory process.<sup>2</sup> It remains a challenge to identify morphologic and molecular markers able to discriminate vulnerable plaques from stable ones, allowing for risk stratification and preventing measures for patients at high risk for acute CV events before they develop. To date, only high-intensity statins have proven as most effective approaches to stabilize atherosclerotic plaque and improve the cardiovascular outcome; PCSK-9 inhibitors, albeit much more expensive agents, are also moving in the same direction.<sup>36</sup> Whether pure anti-inflammatory agents, as heralded by the results of the CANTOS trial, might also be efficacious in this regard awaits confirmation by ongoing and future studies.

### **Conclusion and Perspective**

The CANTOS trial showed for the first time that antiinflammatory therapy targeting the interleukin-1 $\beta$  innate immunity pathway with subcutaneous injections of canakinumab every 3 months led to a significantly lower rate of recurrent CV events than placebo, independent of lipid-level lowering, in patients with prior MI. Interestingly, cancer, particularly lung cancer, mortality was significantly lower with canakinumab than with placebo. The announcement and concurrent publication of the results of this trial stirred excitement and hype about a

“wonder” new drug to combat atherosclerosis. However, major caveats need to be considered including the fact that cardiovascular mortality was not affected, the incidence of fatal infections was much higher with the drug compared with placebo, and the cost of this therapy remains currently prohibitive for wider use. Importantly, the decrease in the risk for the composite primary end point (nonfatal MI, nonfatal stroke, and CV death) was only modest (15%) compared with placebo, and, although statistically significant ( $p=0.02075$ ),<sup>6</sup> it remains dubious whether this effect may prove to be clinically significant. Ongoing and future trials with similar or more convenient and less expensive anti-inflammatory agents may provide more data whether such results are reproducible and/or supportive or evidential of the inflammatory hypothesis of atherosclerosis. Finally, new emerging fields, such as nanotechnology and nanomedicine, may provide new means for advanced imaging and therapy of cardiovascular disease, including atherosclerosis.<sup>37</sup>

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**Table 2. Clinical Trials Examining the Role of Inflammation in Cardiovascular (CV) Risk**

Clinical Trial / Year	Aim	Rx	Outcome
PROVE-IT - TIMI 22/ 2005 <sup>8</sup>	To examine if intensive lowering of LDL cholesterol could reduce the risk of CV events in pts who had sustained an acute coronary syndrome	Statins (atorva statin / prava statin)	Reduction in both LDL cholesterol and hsCRP levels was predictive of a significant reduction in CV events
JUPITER / 2008 <sup>9</sup>	To examine if hsCRP testing could identify the patients who remained at risk among those who have normal or low levels of LDL cholesterol, and, if statins could reduce the risk of heart attack and stroke in these patients	Rosuva statin	Benefit in pts with no CV disease, no diabetes, and 'acceptable' levels of LDL cholesterol, suggesting that lowering levels of inflammation may reduce CV events
IMPROVE -IT / 2015 <sup>38</sup>	To examine the role of dual targets by lowering both LDL cholesterol and hsCRP	Simva statin or ezetimibe /simva statin	LDL cholesterol and hsCRP lowering was associated with improved CV outcomes
CANTOS / 2017 <sup>6</sup>	To examine the role of anti-inflammatory treatment on CV risk	Canakinu mab	Reduced CV risk in pts with a prior MI

CV = cardiovascular; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MI = myocardial infarction; pts = patients; Rx = treatment

**Table 1. Anti-inflammatory Agents with Potential Cardioprotective Effects**

Agent	Mode of action	Studies
Colchicine	Inhibition of activated neutrophils	Nidorf et al
Anakinra	IL-1 receptor antagonist	<b>MRC-ILA Heart Study</b>
Inclacumab	P-selectin blockade	SELECT-ACS / SELECT-CABG
Atreleuton	5-lipoxygenase inhibitor	VIA-ACS
Methotrexate	Decrease in IL-1, IL-6, TNF $\alpha$ production	CIRT
Canakinumab	IL-1 $\beta$ blockade	CANTOS