The CANTOS Trial

One Important Step for Clinical Cardiology but a Giant Leap for Vascular Biology

Richard A. Baylis, Delphine Gomez, Ziad Mallat, Gerard Pasterkamp, Gary K. Owens

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The importance of inflammation in atherosclerosis has been a topic of basic research for several decades. However, despite a clear link between inflammation and atherosclerosis in contemporary vascular biology, clinical data demonstrating a direct benefit of targeting inflammation on patient outcomes have been absent—until now. The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study)[1] was a randomized, double-blinded, placebo-controlled trial that investigated the use of canakinumab, a monoclonal antibody targeting IL (interleukin)-1β, on high-risk patients with established atherosclerotic disease who had already survived a myocardial infarction (MI). To be included in the trial, each patient needed to have residual inflammatory risk, meaning that subjects had elevated biomarkers of inflammation despite standard of care therapy. The treatment was administered quarterly at 3 different doses (50, 150, and 300 mg). All doses significantly lowered the inflammatory burden (a 26%, 37%, and 41% reduction in hsCRP [high-sensitivity C-reactive protein] for the corresponding doses) and, importantly, had no impact on LDL (low-density lipoprotein) cholesterol. However, only the 150-mg dose succeeded in reducing the primary end point (nonfatal MI, stroke, or cardiovascular death) by 15% (P=0.02074) meeting the trial's prespecified significance threshold of 0.02115. The overall effect was a reduction in the incidence of a recurrent cardiovascular event from 16% in the placebo-treated group to 14% in the 150-mg canakinumab group during the median 3.7-year follow-up. Interestingly, this outcome was primarily the result of reduced recurrent MI with no significant change in nonfatal stroke, cardiovascular death, or all-cause mortality. The latter was because of offsetting effects of reduced cancer mortality but increased fatal infections. Therefore, as suggested in an insightful editorial,[2] by Harrington, despite CANTOS being the first study to show that targeting inflammation can confer modest cardiovascular benefit in very high-risk patients, the safety concerns and potentially prohibitive cost make it unclear whether canakinumab will ultimately be used as a secondary prevention after MI. Nevertheless, the results do provide an exciting glimpse at the potential for using anti-inflammatory therapies for treating cardiovascular disease. However, to do so, we must (1) identify safer and more efficacious strategies before considering widespread use of anti-inflammatory therapies to lower-risk patients; or (2) find ways to identify subsets of patients who will derive maximum benefits from canakinumab (or other anti-inflammatory agents) but who are at low risk for serious infections. We feel that the best path toward achieving this goal is to increase our basic understanding of not only the negative but also the potential positive roles of inflammation in atherosclerosis. In this rapid review, we will critically evaluate the CANTOS results and try to identify the challenges facing the vascular biology field moving forward.

Interpreting the Mode of Lesion Failure

Although not reported in the original article,[1] it would be interesting to know what subset of MI was benefited (ST-segment–elevation or non–ST-segment–elevation MI), which could give us a hint as to the modus of atherosclerosis complication. Specifically, whether the canakinumab-treated patients were more protected from plaque erosion or plaque rupture events. In CANTOS, 91% of patients were on statin therapy and the mean LDL cholesterol was relatively well controlled at 82 mg/dL. Current literature would suggest that these factors may skew these patients to be at relatively higher risk for plaque erosion rather than rupture.[3] Further evidence for this trend may be gleaned from the more statistically robust results when unstable angina with urgent revascularization was included in the analysis, suggesting that partially occlusive events like non–ST-segment–elevation MI and unstable angina may have disproportionately benefited. Unfortunately, our current experimental models in hypercholesterolemic mice fail to emulate many of the key features of plaque erosion (ie, endothelial desquamation, neutrophil recruitment, few macrophages, and small necrotic core).[4] However, a recent study found that a combination of vascular injury followed by flow disruption recapitulated many of the characteristics of eroded plaques, a strategy that may be a valuable tool to probe anti-inflammatory therapies moving forward.[5] It is important to note that even if there were a trend toward reduced relative risk of plaque erosion in these patients, plaque rupture of thin-capped fibroatheromas—also known as vulnerable plaques—remains the primary modality for atherosclerosis complications and still requires extensive research focus. Estimates on the prevalence

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of plaque erosion and rupture vary, but even aggressive estimates suggest that rupture remains the primary driver of plaque failure. Indeed, a ruptured fibrous cap is found in approximately two-third of postmortem samples from patients dying of an acute coronary syndrome[4] and intravascular imaging has shown that plaque rupture accounts for ≈71% and 43% of ST-segment–elevation or non–ST-segment–elevation MI, respectively.[3] Although the PROSPECT study (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) showed that only 5% of thin-capped fibroatheromas resulted in a clinical event in 3.4 years, thin-capped fibroatheroma plaque morphology was the only independent risk factor that was predictive for a future event.[6] This latter observation emphasizes the point that major adverse cardiovascular events are relatively rare, but they are still much more likely to occur at high-risk thin-capped fibroatheromas. As an analogy, being struck by lightning may be an extraordinarily rare event, but it is still unwise to hold a metal rod in the air during a lightning storm. Both modes of lesion failure have critical clinical importance, and although it is suggested that over time erosion is becoming more prevalent as a pathological substrate of an acute MI,[3] it is too soon to write off rupture such that future studies of potential anti-inflammatory agents need to examine both of these processes.

Preclinical Study of Residual Inflammatory Risk

Another interesting characteristic of the CANTOS trial that alludes our current preclinical models is the concept of residual inflammatory risk.[7] Lipid-lowering therapies are the mainstay for treating patients at high-risk for cardiovascular disease, and pioneering results from several large-scale clinical trials suggest that most patients with cardiovascular disease should be on high-intensity statin therapy, meaning that the average patient has more than a 50% reduction in their LDL cholesterol level.[8,9] In addition, these studies revealed a potent anti-inflammatory benefit of statin therapy. However, despite the potent benefit of high-intensity statins, there are subsets of patients who retain elevated levels of inflammatory biomarkers like hsCRP, which portend a high risk for future clinical events. This scenario is referred to as residual inflammatory risk and falls in stark contrast to our cholesterol-driven mouse models of atherosclerosis, which require simultaneous genetic and dietary manipulations to induce extraordinarily high cholesterol levels. Therefore, apart from the inflammation caused by excessive cholesterol burden, current mouse atherosclerosis models in general fail to adequately mimic the elevated systemic inflammation that defines this patient population. One possible course would be to further manipulate mice to more closely match the clinical situation (eg, inciting inflammation with surgically induced MI or chemically induced peritonitis), but no matter how hard we try, our mice will remain mice. Key barriers include (1) the many obvious differences between mice and humans (eg, genetics, immune systems, diet, lifespan, microbiomes, and comorbidities); (2) the timeline of years to decades of atherosclerosis development, progression, and treatment in humans versus weeks to months in our mouse models; and (3) an inability to account for effects of current treatments in humans including aggressive lipid-lowering, antithrombotic therapies, and anti-ischemic interventions (ie, coronary bypass or angioplasty). Indeed, as clinical trials further select for the highest risk patient subsets, our animal models are likely to become increasingly incapable of properly modeling their complications even with heroic well-intended efforts.

Nevertheless, our simplified models can be extremely valuable for testing hypotheses that derive from human studies and clinical trials such as CANTOS and for attempting to identify new and more effective therapeutic targets. However, the CANTOS trial results further drive home the need for us to continue to try to better match animal models to the cardiovascular disease and clinical need of interest and for investigators to put much more emphasis on performing human validation studies. For example, we recently used a novel single-cell epigenetic method developed in our laboratory to show that nearly a third of the cells within advanced human coronary artery lesions presumed to be macrophages based on expression of CD68 are actually of smooth muscle cell (SMC) rather than of myeloid origin thus validating our initial discovery of SMC-derived macrophage-like cells observed in SMC lineage-tracing mouse studies.[10] Indeed, the results of CANTOS need to drive hypotheses for future animal studies aimed at identifying better therapies for treating advanced atherosclerosis.

Determining the Mechanism of the Benefit

As we continue to probe for mechanisms by which neutralizing IL-1β improved cardiovascular outcomes, fundamental questions remain. For example, it is unclear whether the benefits were driven by reductions in systemic inflammation or locally within the plaque. The systemic effect of IL-1β neutralization could manifest as improved metabolic parameters, reduced platelet activation, or leukocyte mobilization from the bone marrow. Indeed, in the Novartis press release on August 27 (https://www.novartis.com/news/media-releases/novartis-phase-iii-cantos-study-demonstrates-targeting-inflammation-acz885), they reported no benefit on new onset diabetes mellitus. However, there is a large body of preclinical evidence to suggest an overall benefit of inhibiting IL-1 signaling on pancreatic islet health and homeostasis[11] although as yet data are unclear as to whether canakinumab treatment confers improved glycemic control and insulin sensitivity, and if so, in what patient populations.[12,13] In addition, a previous study by Sager et al[14] showed reduced post-MI leukocytosis when mice were given a murine version of canakinumab. Despite well-characterized benefits systemically, there exists a paucity of information on the impact of IL-1β neutralization on the lesions themselves, particularly on key cell types thought to regulate plaque stability (ie, SMC, macrophage, and endothelial cells). A study from our laboratory using global IL-1 receptor 1 knockout mice suggested that IL-1 signaling promoted several beneficial processes during atherosclerosis development including collagen synthesis and SMC investment into the fibrous cap.[15] However, we still do not know the impact of disruption of IL-1 signaling on established atherosclerotic lesions and there remains a lot of confusion about how different lesion cell types may respond. For example, in the discussion of the CANTOS results, the authors highlight

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one of the roles for IL-1 signaling is to promote SMC proliferation, a process that we believe has been incorrectly assumed by many in the field to be detrimental. We believe that this concept resulted from an inappropriate extrapolation of early studies of in-stent restenosis where SMC proliferation would eventually result in vessel stenosis and the need for revascularization. However, this interpretation is not applicable to advanced atherosclerotic lesions where SMC enrichment—especially within the fibrous cap—is universally considered beneficial. However, even this interpretation is overly simplistic, as we now have good evidence that SMC can perform a multitude of functions within the lesion and that their overall impact on lesion stability can be beneficial or detrimental depending on the nature of their phenotypic and associated functional transitions.[16–18] However, this confusion highlights the critical need for increased understanding of the impact of anti-inflammatory strategies on all major lesion cell types and, especially, on extracellular matrix-producing cells responsible for forming a protective fibrous cap.

Avoiding the Adverse Effects of Anti-Inflammatory Therapies

The IL-1β signaling pathway and inflammation are critical for many protective processes including infection and wound healing that clearly did not evolve to increase our risk of cardiovascular disease. Instead, it is the dysregulation of well-intended processes like oxidized-lipid clearance and macrophage egress that promotes atherosclerosis.[19–22] Thus, assuming IL-1 signaling regulates both detrimental and beneficial processes may help explain both the modest overall benefits of canakinumab and the interesting dosing effects. Specifically, the cancer data published in the Lancet[23] and the rate of infections show clear dose-dependent changes with IL-1β neutralization, suggesting that IL-1 signaling is not saturated. In contrast, the cardiovascular benefit failed to show a similar dose response for cardiovascular outcomes (ie, the 150- and 300-mg doses resulted in equivocal results). The failure of the 300-mg dose to reach statistical significance is, in part, because of complicated hierarchical statistical analyses, but a closer look reveals that several of the outcome measures actually fared worse at the highest dose (eg, MI had a relative risk reduction of 24% at 150 mg and 16% at 300 mg). It is therefore possible that at this dose, the benefit of inhibiting harmful inflammatory processes is offset by also preventing beneficial ones. Indeed, this is reminiscent of a previous murine study testing IL-1β neutralization at 3 different doses on atherosclerosis development in which they also found that beneficial changes in lesion characteristics (ie, CD68 and lipid staining) only occurred at the middle dose of treatment.[24] This highlights that we still have a lot to learn about the processes regulated by inflammation and places the onus on vascular biologists to determine strategies that inhibit the detrimental effects of inflammation while retaining and promoting the beneficial processes. In this regard, modulation of antigen-specific adaptive immune responses may be well suited to selectively target proatherogenic responses while preserving other protective processes like host-defense and wound healing.

Identifying Responder From Nonresponders

The CANTOS authors note that if patients are divided at the median of hsCRP response, the patients that fall in the upper half of hsCRP reduction—the responders—had a 27% reduction in cardiovascular events compared with only 5% for the lower half. The authors suggest that a trial dose of canakinumab could be used to determine whether a patient has adequate hsCRP reduction to justify continuing their treatment. However, the problem is more complex than this—we must also be able to identify those most at risk for the potential harmful effects of anti–IL-1β treatment including fatal infection. As such, a challenge for future studies is to determine genetic and epigenetic mechanisms that influence responsiveness to anti–IL-1β treatment and other screening methods (eg, more informative biomarkers) that can better identify which patients will benefit and which will not. One intriguing possibility was recently identified by Fuster et al[25] who studied how mutations in hematopoietic stem cells that contribute to clonal selection in elderly individuals can significantly impact atherosclerosis development by modifying the function of myeloid cells. Of major interest, they showed that one of the most prevalent mutations in human hematopoietic stem cells, Tet2, could drive clonal selection in LDL receptor knockout mice. Interestingly, these mutations markedly exacerbated atherosclerosis development, which was accompanied by enhanced IL-1β production by macrophages. As we look to the future, it will be interesting whether this becomes a part of our personalized approaches to cardiovascular care, where patients with proatherogenic clonal hematopoiesis are more aggressively targeted with anti-inflammatory medications. Obviously, this is just one of many other possibilities to consider.

Looking for Benefits in Other Disease Contexts

Inflammation has been implicated in a diverse array of human pathologies. Perhaps the most exciting observation of CANTOS is the 77% reduction in lung cancer fatality.[23] Although previous cancer diagnosis was among the exclusion criteria for the trial, the age and medical history of the patients put them at high risk for cancer development and consequently 6.5% of patients were diagnosed with cancer during the trial. For example, the patients who eventually developed lung cancer had an average age of 65 years and >90% had a smoking history. Indeed, cardiovascular disease and certain cancers share a host of risk factors including elevated hsCRP. The authors suggest that the benefit was unlikely because of preventing new cancers but rather inhibiting the progression and eventual metastasis of previously undiagnosed cancers. The results will need to be repeated in a formal cancer clinical trial, but these initial data are exciting. Perhaps this reveals an important lesson for researchers that as we continue to make progress on anti-inflammatory therapies for cardiovascular disease, we should be vigilant for data that may support a benefit of therapy in another disease context. It is a provocative concept that one preventative medication could yield protection from an array of human diseases—perhaps this is the best chance for canakinumab. Patients at high risk of lung cancer could be treated and be promised both a profound

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benefit for cancer mortality and also reduced risk for cardiovascular disease.

In summary, the CANTOS trial is an exciting conclusion to the first chapter of a decades-long investigation of the inflammatory hypothesis of atherosclerosis. Thanks to the seminal work from many pioneering vascular biologists, clinical trialists, and Novartis, we have clinical outcome data showing a clear benefit of targeting inflammation in high-risk patients with cardiovascular. However, many large questions remain—what is the impact of canakinumab on plaque stability, how can we avoid inhibiting beneficial inflammatory processes like host defense, how can we better identify patients that would most benefit from these therapies? The pursuit of these questions will hopefully reveal more efficacious and safer therapies. For now, we must celebrate this trial for its significant scientific impact, having revealed inflammation as a viable and likely fertile path toward improved atherosclerosis management but commit ourselves to better understanding the vascular impacts of targeting inflammation.

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Disclosures

The Owens Laboratory has collaborated with Novartis to study the impact of an IL-1β neutralization on atherosclerosis in mice.

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