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Moving Beyond JUPITER: Will Inhibiting Inflammation Reduce Vascular Event Rates?

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Abstract

The recent JUPITER trial demonstrated that potent statin therapy reduces by 50 percent the risk of heart attack and stroke among men and women with low levels of LDL-cholesterol who are at increased vascular risk due to elevated levels of CRP, a biomarker of low-grade systemic inflammation. In JUPITER, both absolute risk and the absolute risk reduction with statin therapy in JUPITER were related to the level of CRP whereas no such relationship was observed for LDL-C. Further, on-treatment levels of CRP and LDL-C were independently associated with residual risk, and the genetic determinants of statin-induced CRP reduction differed from the genetic determinants of statin-induced LDL reduction. Despite these data, it is impossible in any statin trial to establish whether the clinical benefits of treatment are due to LDL-reduction alone, to inflammation inhibition, or to a combination of both processes To address the hypothesis that lowering inflammation will lower vascular event rates, two large-scale placebo controlled trials using targeted anti-inflammatory agents for the secondary prevention of myocardial infarction have been initiated. The first trial, the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) is evaluating whether interleukin-1β (IL-1β) inhibition as compared to placebo can reduce rates of recurrent myocardial infarction, stroke, and cardiovascular death among stable coronary artery disease patients who remain at high vascular risk due to persistent elevations of hsCRP (≥2 mg/L) despite contemporary secondary prevention strategies. The second trial, the Cardiovascular Inflammation Reduction Trial (CIRT) has been funded by the NHLBI and will evaluate whether low dose methotrexate (target dose 20 mg/week) as compared to placebo will reduce major vascular events among a group of post-myocardial infarction patients with either diabetes or metabolic syndrome, groups known to have high risk on the basis of a persistent pro-inflammatory response. Together, CANTOS and CIRT represent a core test of the inflammation hypothesis of atherothrombosis and the exploration of a potential new phase for cardiovascular therapeutics.

Keywords

inflammation; clinical trials; C-reactive protein; Interleukin-1; atherosclerosis; diabetes; statin therapy

Introduction

The recent JUPITER trial demonstrated that potent statin therapy can cut by half the risk of future heart attack and stroke among men and women with low levels of LDL-cholesterol who are at increased vascular risk due to elevated levels of CRP, a biomarker of

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inflammation. Further, in JUPITER, the absolute risk reduction attributable to statin therapy increased with increasing levels of baseline inflammation. However, whether directly targeting inflammation can reduce vascular risk remains uncertain and two large-scale placebo controlled trials – CANTOS and CIRT – have recently been initiated to address this issue. In this review, a discussion of clinical information linking inflammation to atherothrombosis is followed by an examination of the JUPITER trial to dissect whether the benefits observed were due to LDL-C reduction alone or to a combination of lipid lowering and inflammation inhibition. Finally, the core rationale and design features of the CANTOS and CIRT trials will be described.

Clinical Evidence Linking Inflammation and Atherothrombosis: From Basic Biology to JUPITER

Laboratory evidence has long indicated that inflammation plays crucial roles in all stages of the atherothrombotic process1. Clinically, translation of the inflammatory hypothesis of atherosclerosis to practice has been based on observational evidence linking inflammatory biomarkers such as high sensitivity C-reactive protein (hsCRP)2,3 to the risk of future vascular events. As shown in recent meta-analysis, the magnitude of cardiovascular risk associated with a one standard deviation increase in hsCRP is at least as large as that associated with a one standard deviation increase in either total cholesterol or blood pressure4. Further, the addition of hsCRP, along with family history, improves global risk prediction and is the basis for the commonly used Reynolds Risk Score5 (www.reynoldsriskscore.com) which has recently shown superior discrimination and calibration when compared to the Framingham Risk Score in external validation6.

To date, the use of hsCRP as a method to improve targeting of drug therapy has primarily come in the context of statin prescription. Following observations that statins reduce hsCRP in an LDL-independent manner and that the magnitude of statin benefit is greater among those with inflammation7,8, the observation was made in several trials that lower levels of hsCRP following statin therapy correspond to lower levels of risk9–13. As such, statins were hypothesized to be “two-fers” that potently reduce LDL-C and have potentially relevant anti-inflammatory effects. On that basis, the JUPITER trial was designed to address whether individuals who would never qualify for statin therapy due to already low levels of LDL-C might benefit from treatment if they had evidence of an enhanced inflammatory response as determined by hsCRP > 2 mg/L14.

In brief, in January of 2003, the JUPITER investigators began to enroll 17,802 men and women with no evidence of cardiovascular disease and normal to low levels of LDL cholesterol into a controversial trial testing whether individuals with an enhanced inflammatory response might benefit from aggressive statin therapy using a regimen of rosuvastatin 20 mg po daily. At study entry, the mean LDLC level for enrolled participants was just above 100 mg/dL, nearly half had Framingham scores of 10 percent or less, and none were considered candidates for statin therapy under any current set of prevention guidelines. However, all trial participants had levels of the inflammatory biomarker hsCRP ≥ 2 mg/L, putting them at elevated risk for future cardiovascular disease. Reflecting the investigators interest in evaluating patient groups under-represented in prior statin trials, JUPITER enrolled 6801 women, 5695 participants age 70 or over, and more than 5000 non-Caucasians.

As reported in 200814, random allocation to rosuvastatin 20 mg as compared to placebo within the JUPITER population resulted in a 54 percent reduction in myocardial infarction (P=0.0002), a 51 percent reduction in ischemic stroke (P=0.004), a 46 percent reduction in need for bypass surgery or angioplasty (P<0.0001), and a 20 percent reduction in all-cause

mortality (P=0.02). For the JUPITER primary endpoint of major arterial vascular events, the P-value for the overall 44 percent relative risk reduction was <0.0000001. Effects were similar for women as for men, for the elderly, among those with and without metabolic syndrome, hypertension, or obesity, and in all ethnic groups15–16. Overall, in this trial that targeted those with underlying evidence of inflammation, the Number Needed to Treat (NNT) for those with low levels of LDLC but elevated hsCRP was smaller than the NNT for the treatment of dyslipidemia or high blood pressure in comparable primary prevention patients17. On the basis of these data, national guidelines in several countries have endorsed the use of statin therapy in primary prevention among those with elevated hsCRP18, and the United States Food and Drug Administration formally expanded the labeling of statin therapy to include those with elevated hsCRP and at least one additional risk factor, even if LDL-C levels are already low.

LDL-C Reduction, Inhibition of Inflammation, or Both?

Several additional analyses from JUPITER merit consideration as investigators try to understand whether the observed effects are due only to LDL-C reduction or if they might also relate, at least in part, to anti-inflammatory effects.

First, on a pre-specified basis, the JUPITER investigators also reported that rosuvastatin was associated with a 43 percent reduction in venous thromboembolism (P=0.007)19. This observation is relevant since LDL-C is not a major determinant of venous thrombosis and there is no plaque in the veins to rupture. Yet, inflammation is highly relevant to *in situ* thrombosis and thus the LDL-independent effects observed for rosuvastatin on clotting and thrombosis are consistent with the possibility of direct anti-inflammatory benefit, at least on the venous side of the circulation.

Second, as seen in the PROVE-IT, A to Z, REVERSAL, and ASCOT13 trials, those who achieved low levels of hsCRP while on rosuvastatin in JUPITER also achieved the greatest levels of risk reduction20. Further, in JUPITER as in earlier studies, the magnitude of hsCRP reduction could not be predicted on the basis of the magnitude of LDL-C reduction.

Third, in gender stratified analyses, both the absolute risk of events in the placebo group and the absolute risk reduction associated with rosuvastatin was greater among those with higher levels of CRP at study entry, an effect not observed for LDL-C21.

Fourth, in a series of genetic analyses using genome wide association study, the genetic determinants of rosuvastatin-induced LDLC reduction in JUPITER were found to differ from the genetic determinants of rosuvastatin-induced CRP reduction. Thus, separate and unrelated pathways appear to impact on statin-induced changes in lipids as compared to inflammatory mediators22,23.

All of these findings are consistent with the hypothesis that part of the statin benefit observed in JUPITER was due to effects that go beyond simple reduction in LDL-C. However, because statins potently lower LDL-C, no statin trial can definitively address whether lowering inflammation *per se* will reduce vascular events. Yet, the clinical, laboratory, genetic, and pathologic data that derive from the statin literature provide the core basis for proceeding with a series of “cardiovascular inflammation reduction trials” designed to test directly whether specific anti-inflammatory agents without confounding effects on cholesterol can reduce cardiovascular events24.

Moving Beyond JUPITER Part I: CANTOS and Canakinumab

In the past year, our research group has initiated two hard-endpoint clinical trials designed to address whether targeting inflammation directly will improve vascular outcomes.

The first trial, the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) is supported by Novartis and is evaluating a human monoclonal antibody that targets interleukin-1β (IL-1β)25. Of inflammatory cytokines implicated in atherothrombosis, interleukin-1 plays an important role as cholesterol crystals can activate the NLRP3 inflammasome which results in cleavage of pro-interleukin-1β into locally secreted IL-1β, in turn triggering a pro-inflammatory response26,27. IL-1β activates hepatic production of IL-6 which ultimately leads to increased production of inflammatory acute phase reactant biomarkers including CRP. Intact mechanisms for macrophage autophagy also appear to play a role in regulating activation of the NLRP3 inflammasome by cholesterol crystals. In recent work, macrophage specific deletion of the essential autophagy gene ATG5 resulted in inflammasome activation and an increased burden of cholesterol crystals within atherosclerotic plaques28. These data raise the hypothesis that defective macrophage autophagy may result in unopposed cholesterol crystal-induced IL1-β release and subsequent promotion of atherogenesis.

Once activated, IL-1 can induce monocyte and leukocyte adhesion in human vascular endothelial cells29,30. Reduced lesion formation has been reported in atherosclerosis-prone mice deficient in either IL-1 or the type I IL-1 receptor, and studies performed on pig coronary arteries show increased neointimal formation with administration of IL-1 and reduced neointima formation in the presence of IL-1 receptor antagonism31,32. Human studies supporting these concepts include observations that atherosclerotic coronary arteries have increased IL-1β levels, that IL-1Ra concentrations are higher among those with acute coronary syndromes, and that polymorphism in IL-1Ra associates with number of coronary lesions on angiography. Thus, inhibition of IL-1β has been hypothesized to have a beneficial effect on multiple pathways associated with atherosclerosis and its progression30.

CANTOS has been designed to directly address the hypothesis that IL-1β inhibition with canakinumab, a human monoclonal anti-human IL-1β antibody, might serve as a novel treatment to reduce cardiovascular event rates25. Canakinumab directly binds human IL-1β and thus blocks the interaction of this cytokine with its receptors. In patients with type 2 diabetes, IL-1β antagonism with canakinumab produces a rapid and dose-dependent inhibition of the acute phase response resulting in sustained reductions in fibrinogen, IL-6, and CRP without impacting on lipid levels and with marginal effects on mediators of insulin resistance.

Formally, CANTOS is evaluating whether long-term treatment with canakinumab as compared to placebo will reduce rates of recurrent cardiovascular events among stable post-myocardial infarction patients who remain at elevated vascular risk due to persistently elevated levels of hsCRP (≥ 2 mg/l) despite usual care, including statin therapy. CANTOS will evaluate three active doses of canakinumab (50 mg, 150 mg, or 300 mg SC every three months) in comparison to placebo. The trial primary endpoint will be recurrent major cardiovascular events, defined as non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. Secondary objectives of CANTOS include determination of the safety and efficacy of long-term canakinumab therapy and on other vascular events associated with inflammation. Further, among those with normal or impaired fasting glucose at the time of randomization, CANTOS will also address whether canakinumab will reduce the incidence of new onset diabetes.

CANTOS began enrollment in late 2011 and ultimately will include 17,200 adult men and women who have suffered a documented acute myocardial infarction at least 30 days before randomization, have completed any planned revascularization procedures associated with their initial infarction, and have evidence of systemic inflammation on the basis of an hsCRP ≥ 2 mg/L despite the stable use of standard secondary prevention therapies. As canakinumab is an inhibitor of innate immunity, patients with a suspected or known immuno-compromised state, those taking another biologic agent that targets the immune system (TNF blockers, anakinra, rituximab, abatacept, tocilizumab), those already taking methotrexate at a dose exceeding 15 mg weekly, and those with a history of or at high risk for tuberculosis or HIV related disease will not be eligible.

Moving Beyond JUPITER Part II: CIRT and Low-Dose Methotrexate

The second trial we have initiated is the NHLBI-sponsored Cardiovascular Inflammation Reduction Trial (CIRT) that is evaluating the role of low-dose methotrexate as a potential anti-inflammatory agent to suppress cardiovascular event rates24.

Low-dose methotrexate (target dose range 15 to 20 mg per week) is commonly used as the treatment of choice for rheumatoid arthritis and psoriasis, patient groups known to have elevated risks for cardiovascular disease. As methotrexate is a generic agent with nearly 40 years of clinical experience, guidelines from the American College of Rheumatology provide clear data regarding dosing regimens, drug monitoring, and the identification of high-risk patient subgroups33. While low-dose methotrexate reduces inflammatory biomarkers including CRP and IL-6 in patients with rheumatoid arthritis, low-dose methotrexate does not have any major effects on lipid levels. As such, like canakinumab, low-dose methotrexate provides a therapeutic method to test the inflammatory hypothesis of atherothrombosis without confounding effects on plasma lipid levels.

The CIRT is based both on available observational evidence that those taking the drug have lower vascular event rates, and on experimental data suggesting that methotrexate reduces vascular lesion formation in animal models.

With regard to observational evidence, a series of case control and prospective cohorts of patients with rheumatoid arthritis and psoriatic arthritis have found that those given low dose methorexate have reduced rates of myocardial infarction and vascular death, even though those receiving low-dose methotrexate often had worse vascular risk factor profiles34. In a recent meta-analysis of these studies, low-dose methotrexate was associated with a 21 percent lower risk for total cardiovascular disease and an 18 percent lower risk of myocardial infarction with only modest evidence of between-study heterogeneity35. Other observational studies of rheumatoid arthritis patients taking low-dose methotrexate have shown improvement in heart failure and reduction in carotid intima media thickness36. The observation that acute myocardial infarction mortality has declined as anti-inflammatory therapy has become more widespread for rheumatoid arthritis is consistent with these data37.

With regard to experimental data, mechanistic studies suggest that atheroprotective effects of low-dose methotrexate may accrue in part from enhanced release of adenosine and a consequent facilitation of cholesterol efflux and reverse cholesterol transport from arterial wall foam cells via upregulated expression of cholesterol 27-hydroxylase (HY27) and the ATP-binding cassette transporter (ABCA1)38,39. Low-dose methotrexate also appears to have effects on apoptosis and on the suppression of adhesion molecule function. Recently, Bulgarelli and colleagues have shown that methotrexate inhibits atherogenesis in cholesterol fed rabbits40; specifically, in New Zealand rabbits fed a 1% cholesterol diet for 60 days, metotrexate reduced lesion areas by 75 percent and reduced the intima-media ratio 2-fold. In

these studies, methotrexate also inhibited macrophage migration to the intima and markedly reduced apoptotic cell accumulation and migration. All of these effects are consistent with anti-atherosclerotic actions for low-dose methotrexate.

CIRT will formally test whether low-dose methotrexate can reduce rates of recurrent myocardial infarction, stroke, and cardiovascular death among stable post-myocardial infarction patients with type 2 diabetes or metabolic syndrome, conditions associated with an enhanced pro-inflammatory response. CIRT is a randomized, double-blind, placebo-controlled, multi-center, event-driven trial that will enroll 7,000 men and women from the United States and Canada. Following a five-week open-label run-in, eligible participants who have suffered documented myocardial infarction in the past five years will be randomly allocated to usual care plus placebo or usual care plus low-dose methotrexate (initial target dose 15 mg po per week with a safety-based titration to 20 mg po per week after 4 months based on evidence of safety and tolerability). All study participants will additionally receive 1 mg daily oral folate. Low-dose methotrexate complications will be minimized through education programs for all investigators and coordinators, through enhanced communication with study participants, by limiting enrollment to those with no evidence of malignancy, hepatitis, renal dysfunction, chronic infection, or other methotrexate risk factors; and through regular monitoring of liver function and hematologic indices using a centralized methodology.

The primary trial endpoint of CIRT is the rate of recurrent myocardial infarction, stroke, or cardiovascular death. As in CANTOS, secondary endpoints include all-cause mortality, additional vascular disorder associated with a proinflamamtory state, and incident diabetes among those with metabolic syndrome at study entry. This latter issue is based on evidence indicating a major role for inflammation in diabetes.41

Conclusion

Taken together, CANTOS and CIRT provide the clinical community with two “swings of the bat” to address whether reducing inflammation can reduce vascular event rates. Each trial employs an event driven protocol to address whether a broad spectrum anti-inflammatory (low-dose methotrexate) or a targeted vascular anti-inflammatory (cankinumab) as compared to placebo can reduce rates of recurrent myocardial infarction, stroke, and cardiovascular death among stable coronary artery disease patients who remain at risk due to a persistent pro-inflammatory response.

Sites in the United States or Canada interested in participating in CANTOS or CIRT can get further information at theCANTOS.org and theCIRT.org websites, or by calling (855) 437-9330. Information on both trials is also available at ClinTrials.gov.

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