Editorial

The Canakinumab Antiinflammatory Thrombosis Outcome Study trial—the starting gun has fired

David Crossman[1], Alexander Rothman[2]

[1]School of Medicine, University of St Andrews, North Haugh, St Andrews, Scotland; [2]The Medical School, University of Sheffield, Sheffield, England

Correspondence to: David Crossman. School of Medicine, University of St Andrews, North Haugh, St Andrews, Fife, Scotland KY16 9TF. Email: dcc7@st-andrews.ac.uk.

Provenance: This is an invited Editorial commissioned by the Section Editor Hai-Long Dai (Department of Cardiology, Yan'an Affiliated Hospital of Kunming Medical University, Kunming, China).

Comment on: Ridker PM, Everett BM, Thuren T, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31.

Submitted Nov 09, 2017. Accepted for publication Nov 18, 2017.

doi: 10.21037/jtd.2017.11.96

View this article at: http://dx.doi.org/10.21037/jtd.2017.11.96

When teaching clinical undergraduates about the cause of atherosclerosis the lecturer will highlight risk factors such as smoking, hypercholesterolaemia and hypertension that are mutable for therapeutic benefit. If the same lecturer were to be talking to their science laboratory staff they would discuss inflammatory paradigms in the vessel wall that lead to lipid accumulation in monocyte-derived macrophages that become foam cells. Depending upon the local plaque microenvironment and T cell repertoire these monocyte-derived macrophages direct either plaque stability and/or resolution of inflammation through production of smooth muscle cell mitogens or release proinflammatory cytokines, matrix metalloproteinases and express tissue factor that promotes a disorganised, thrombogenic plaque with lesion progression and associated myocardial infarction or stroke (1). A bright student might ask whether the inflammatory process can be altered for therapeutic benefit? Until the recent publication of the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial the answer would have been, no. So, has CANTOS really changed the response to, yes?

The CANTOS investigators tested the hypothesis that inhibiting the action of the cytokine interleukin-1 (IL-1) beta would have beneficial effects on a composite endpoint in patients with a prior myocardial infarction and a high-sensitivity C-reactive protein (hsCRP) level that constituted a vascular risk (≥2 mg/L) (2). Three different doses of the IL-1 beta neutralising antibody Canakinumab were tested against placebo over 48 months. A dose-dependent reduction in hsCRP was demonstrated without significant alteration in lipid levels. There was a dose graded reduction in the primary endpoint of first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death with the pre-specified, complex statistical threshold for primary and secondary endpoints being met with the 150-mg dose. There was no difference in all-cause mortality, however, there was a significant increase in infection-related deaths when all treated patients were compared with placebo.

The CANTOS trial targeted IL-1beta, a highly specific mediator of inflammation. The broader IL-1 signalling family has been a target for therapeutic inhibition in other disease areas, most commonly using the recombinant IL-1 receptor antagonist (IL-1ra) that inhibits both the active agonists in the family (IL-1 alpha and beta). The IL-1ra approach has had a modest benefit in overt inflammatory conditions such as rheumatoid arthritis (3) and a significant effect in anti-inflammatory conditions characterised by over activity of the inflammasome (4). The IL-1 pathway has considerable preclinical data to support its involvement in atherogenesis, the inflammatory response to fat feeding and the response to vessel wall response to injury (5-7). Whilst these studies, conducted as they were in laboratory animals have all been consistent with a hypothesis that IL-1 is atherogenic, human genetic studies

have been less consistent in their results (8,9).

Against this background CANTOS undertook an investigation of inhibition of IL-1beta in patients with prior myocardial infarction and a risk profile similar to prior studies investigating statins for so-called secondary prevention. The selection of IL-1beta inhibition alone (as opposed to dual IL-1alpha and beta inhibition) is one that makes sense in view of knowledge of the IL-1 system. IL-1alpha is a cytokine released at the time of cellular death and IL-1beta one that is released from the inflammasome in an agonist-induced manner. What cannot be answered is whether dual inhibition would have been better (or worse) than the reduction in clinical events demonstrated with IL-1beta inhibition in CANTOS.

CANTOS selected patients with a hsCRP greater than or equal to 2 mg/L rather than all patients with prior myocardial infarction. This inclusion criteria serves to increase inflammatory signalling available for therapeutic modulation, however, the absence of a treated group with a low hsCRP leaves the hypothesis incompletely examined and the question of how such patients would respond to therapy untested. If the hypothetical low hsCRP group had not responded then modulation of an innate inflammatory paradigm in coronary disease would have been proven using the models of vascular inflammation we currently hold. If the hypothetical low hsCRP group had responded in a similar manner as the high hsCRP group it would prove that IL-1beta was important but that hsCRP was not the appropriate biomarker to represent atherosclerotic instability. As such, the dataset is incomplete without a low hsCRP group. Relevant to this issue, the CANTOS investigators published a subset analysis which indicates that benefit was best achieved in patients in whom Canakinumab most effectively suppressed hsCRP (10). Within the limitation of subset analyses these additional data are supportive of the inflammatory hypothesis.

The CANTOS trial does indicate that IL-1beta inhibition reduces hsCRP in patients who entered the study with a hsCRP ≥2 mg/L. We can only speculate what is driving the raised hsCRP (other than IL-1beta). It was tempting to presume that the increased hsCRP would be primarily driven by lipids as the results of some statin trials suggest (11). The findings of CANTOS, however, dissociate lipids from hsCRP, at least in a well-treated group of patients on statins with higher than usual hsCRP levels (median hsCRP at entry was 4.1 mg/L). Nested within this large group of patients were some who by the end of the trial had presented with lung cancer—this group had a hsCRP of 6.0 mg/L at baseline (11). A hypothesis-generating publication from the CANTOS trail has also shown that the group who made a good hsCRP response, classified as a median hsCRP <1.8 at 3 months, had a highly significant reduction in the diagnosis of incident case lung cancer during the trial. More than 90% of CANTOS subjects were current or ex-smokers (12). Therefore, the inflammatory drive in this group of patients is likely to be complex and multifactorial, and the question of the driver of the raised hsCRP (other than IL-1) remains one of speculation.

Outside of overt inflammatory illnesses inflammation is a response that is beneficial to a number of tissue insults. Modulation of inflammation has, with almost all agents used, come at the cost of side effects, either directly attributable to the reduction in inflammation/immunosuppression or off-target effects. One of the earliest described effects of IL-1 is an effect on bone marrow, to which it acts as a haemopoietic growth factor (13,14). Animal experiments consistently demonstrate a fall in white count with IL-1 inhibition. Both neutropenia and thrombocytopenia were detected in treated patients in CANTOS and these findings translated into a small excess on infection-related deaths in the treated group with no overall increase in mortality. The numbers of cases of tuberculosis were very small and equally distributed across groups, however, it should be noted patients at high risk of infection and possible tuberculosis (TB) were excluded from trial entry. There a was also no excess of haemorrhage. These data, whilst not impacting on the testing of an inflammatory hypothesis in atherosclerosis, do impact the likelihood that this therapeutic approach might be implemented in this patient group. The small primary event reduction (about 1 per 100 patient years) with this side effect profile will probably require additional studies and positive data from another patient group with a higher overall event rate. Such an investigation might be prompted by the success of CANTOS.

CANTOS examined the effect of IL-1beta inhibition at least 30 days distant from a myocardial infraction over a 48-month period. Studies of IL-1 inhibition at the time of myocardial infarction have shown that the hsCRP in non-ST elevation (STE) acute coronary syndrome (ACS) patients is dramatically suppressed by IL-1 receptor antagonist (15). Others have shown in small studies of STE ACS patients IL-1 inhibition not only suppressed hsCRP but also had a signal suggesting favourable remodelling of the left ventricle (16-18). The data from CANTOS are for a highly specific group of patients post ACS, but the

question of whether the outcome for IL-1beta inhibition more proximate to the index ACS would be more or less beneficial is one that should be tested in subsequent studies.

IL-1beta inhibition at current market-price is expensive and comes with an infectious side effect profile. Both aspects are presumably cumulative over the duration of therapy. Whilst the study of other secondary preventive therapies in cardiovascular disease have examined interventions over similar durations the implication is that benefits accrue with extended treatment. It is, however, unclear if this is the case for anti-inflammatory therapy in coronary disease. It might be, but an alternative view is that with extended, modern, high-dose statins and angiotensin converting enzyme (ACE) inhibitor treatment, the addition of anti-IL-1beta therapies may not accrue continued benefit. Shorter treatment duration might be possible at the time of heightened risk and plaque instability (as is undertaken with dual anti-platelet therapy post-ACS). Outcome data from patients who discontinued treatment during or after the study might be helpful in this respect but a biological case could be made for studies of shorter duration therapy to assess whether the majority of benefit is accrued in a shorter time frame, presumably with lower cost and reduced incidence of infectious side effects.

There is no doubt that CANTOS is a trial that the cardiovascular world was waiting for with a high level of anticipation, and the positive headline result has not disappointed. It took years and very many statin trials to prove the lipid hypothesis in atherosclerosis and it will take more than CANTOS to prove the inflammatory hypothesis of coronary disease is tractable for patient benefit. More detail is needed from the study and will undoubtedly come from subsequent studies of IL-1 inhibition and other anti-inflammatory agents in both coronary artery disease and a boarder spectrum of potentially inflammatory driven vascular diseases (19-21)—these are very welcome. Is IL-1 beta inhibition in coronary artery disease going to hit the clinic soon? Probably not, but possibly one day. More importantly and pressingly CANTOS has sounded the starting gun for anti-inflammatory therapy in coronary artery disease.

Acknowledgements

Funding: Authors' work in the area has been supported by UK Medical Research Council Experimental Medicine Grant (G0502131), the National Institute for Health Research and a UK Medical Research Council Clinical Research Training Fellowship (AR-MR/K002406/1). A Rothman is supported by a Wellcome Trust Clinical Research Career Development Fellowship 206632/Z/17/Z.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Tabas I, Lichtman AH. Monocyte-macrophages and T cells in atherosclerosis. Immunity 2017;47:621-34.
2. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31.
3. Thompson C, Davies R, Choy E. Anti cytokine therapy in chronic inflammatory arthritis. Cytokine 2016;86:92-9.
4. Moll M, Kuemmerle-Deschner JB. Inflammasome and cytokine blocking strategies in autoinflammatory disorders. Clin Immunol 2013;147:242-75.
5. Chamberlain J, Francis S, Brookes Z, et al. Interleukin-1 regulates multiple atherogenic mechanisms in response to fat feeding. PLoS One 2009;4:e5073.
6. Morton AC, Arnold ND, Gunn J, et al. Interleukin-1 receptor antagonist alters the response to vessel wall injury in a porcine coronary artery model. Cardiovasc Res 2005;68:493-501.
7. Libby P. Interleukin-1 beta as a target for atherosclerosis therapy: biological basis of CANTOS and Beyond. J Am Coll Cardiol 2017;70:2278-89.
8. Interleukin 1 Genetics Consortium. Cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist: a Mendelian randomisation analysis. Lancet Diabetes Endocrinol 2015;3:243-53.
9. Tsimikas S, Duff GW, Berger PB, et al. Pro-inflammatory interleukin-1 genotypes potentiate the risk of coronary artery disease and cardiovascular events mediated by oxidized phospholipids and lipoprotein(a). J Am Coll Cardiol 2014;63:1724-34.
10. Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Available online: https://doi.org/10.1016/S0140-6736(17)32814-3
11. Catapano AL, Pirillo A, Norata GD. Vascular inflammation and low-density lipoproteins: is cholesterol the link? A lesson from the clinical trials. Br J Pharmacol

2017;174:3973-85.
12. Ridker PM, MacFadyen JG, Thuren T, et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:1833-42.
13. Neta R, Sztein MB, Oppenheim JJ, et al. The in vivo effects of interleukin 1. I. Bone marrow cells are induced to cycle after administration of interleukin 1. J Immunol 1987;139:1861-6.
14. Dubois CM, Ruscetti FW, Keller JR, et al. In vivo interleukin-1 (IL-1) administration indirectly promotes type II IL-1 receptor expression on hematopoietic bone marrow cells: novel mechanism for the hematopoietic effects of IL-1. Blood 1991;78:2841-7.
15. Morton AC, Rothman AM, Greenwood JP, et al. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. Eur Heart J 2015;36:377-84.
16. Abbate A, Kontos MC, Grizzard JD, et al. Interleukin-1 blockade with anakinra to prevent adverse cardiac remodeling after acute myocardial infarction (Virginia Commonwealth University Anakinra Remodeling Trial [VCU-ART] Pilot study). Am J Cardiol 2010;105:1371-7.e1.
17. Abbate A, Van Tassell BW, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction [from the Virginia Commonwealth University-Anakinra Remodeling Trial (2) (VCU-ART2) pilot study]. Am J Cardiol 2013;111:1394-400.
18. Abbate A, Kontos MC, Abouzaki NA, et al. Comparative safety of interleukin-1 blockade with anakinra in patients with ST-segment elevation acute myocardial infarction (from the VCU-ART and VCU-ART2 pilot studies). Am J Cardiol 2015;115:288-92.
19. Soon E, Holmes AM, Treacy CM, et al. Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. Circulation 2010;122:920-7.
20. Hernandez-Sanchez J, Harlow L, Church C, et al. EXPRESS: Clinical trial protocol for TRANSFORM-UK: a therapeutic open label study of tocilizumab in the treatment of pulmonary arterial hypertension. Pulm Circ 2018;8:2045893217735820.
21. Pickworth J, Rothman A, Iremonger J, et al.Differential IL-1 signaling induced by BMPR2 deficiency drives pulmonary vascular remodeling. Pulm Circ 2017;7:768-76.

Cite this article as: Crossman D, Rothman A. The Canakinumab Antiinflammatory Thrombosis Outcome Study trial—the starting gun has fired. J Thorac Dis 2017;9(12):4922-4925. doi: 10.21037/jtd.2017.11.96

