

Interleukin-1 beta inhibition with canakinumab and reducing lung cancer—subset analysis of the canakinumab anti-inflammatory thrombosis outcome study trial (CANTOS)

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Provenance: This is an invited Editorial commissioned by the Section Editor Chunlin Ou (Cancer Research Institute of Central South University, China).

Comment on: Ridker PM, MacFadyen JG, Thuren T, *et al.* Effect of interleukin-1 β 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.

Submitted May 31, 2018. Accepted for publication Jul 09, 2018.

doi: 10.21037/jtd.2018.07.50

View this article at: <http://dx.doi.org/10.21037/jtd.2018.07.50>

In the field of cardiovascular disease, the reporting of the Cantos trial was eagerly wait in 2017. It did not disappoint, and we have previously reviewed the cardiovascular implications of IL-1 beta inhibition in patients with cardiovascular risk, defined as a prior myocardial infarction and a hs-CRP >2 mg/L, in this journal (1). Hard on the heels of the main report of Cantos came a publication that reported the reduction of new cases (incident) lung cancers in the group of patients who had received the largest two doses of canakinumab—the IL-1 beta inhibiting antibody that was the therapeutic agent used (2). The report showed that the overall incidence of lung cancers in the follow-up period of 3.7 years (median) was 129 cases, (61 in the placebo group) but was significantly less frequent in the groups receiving the 150 mg dose [28 cases, HR 0.61 (95% CI, 0.39–0.97), P=0.0337] and the 300 mg [14 cases, HR 0.33 (95% CI, 0.18–0.59), P<0.0001]. The effect of the 50mg dose was not significant. In addition to this, lung cancer mortality was significantly reduced in the 300 mg dose [HR 0.23 (95% CI, 0.10–0.54), P=0.0002]. Total cancer mortality was also reduced but non-lung cancer events when analyzed were not significantly different from the placebo treated group.

An effect of an anti-inflammatory on cancer should not necessarily be a surprise. Database searches for “anti-inflammatory and cancer” yield about 3 times more reports than “anti-inflammatory and atherosclerosis” as a search term. Aspirin, taken for several years, seems to

have protective effects against cancer (3). There is intense interest in tumour-associated inflammatory cells, particularly the macrophage (4), which is known to be a significant source of IL-1 beta. Human genetic studies have identified relationships between IL-1 polymorphisms and breast (5) and lung cancer (6-8). Mice with cancer cells introduced into them that carry mutations that reduce the effects of IL-1 have less evidence of tumour progression or metastasis than wild-type mice (9,10). So far so good.

Clinical trials that are placebo-controlled and randomised follow a basic philosophical principle of scientific research described nearly a century ago by Karl Popper, namely, hypothesis falsification (deductive logic), and the consequence that proving a hypothesis is not possible, at least in a single transaction. More elaborate statistical methods have been added since with the aim of excluding bias but the central principle of testing a pre-specified hypothesis runs through this methodology. The natural inclination to gather more information from the vast effort of a large clinical trial which tests a single hypothesis is obvious and has led to subset and post-hoc analysis. Alacrity for this habit, however, has been significantly reduced by the observation that the play-of-chance may result in a significant result just as much as a plausible (inductive logic), and potentially correct, subset. For example, in the ISIS 2 trial of thrombolysis and aspirin in ST-elevation myocardial infarction, which overall showed benefit of these interventions, when analyzed by star-sign

(of birth) revealed a failure of aspirin if born under Gemini and Libra (11). In addition, in other large trials, therapy appears to work in some countries and not others. The practice of subset analysis, however, has not gone away and is given respectability by calling the analysis exploratory or hypothesis generating. The Cantos lung cancer analysis is in this category and interpreting the importance of the observation is based on the plausibility of the effect seen being real. Such plausibility, which argues against the play-of-chance, relies on issues of study size and event number as well as the biology.

Cantos was a large study, selecting patients who had a hs-CRP ≥ 2 . It was performed in individuals who had a history of prior myocardial infarction and, therefore, enriched (without intent) for current or previous smokers. One would expect, therefore, that if there is an anti-cancer effect it would be seen in a smoking-associated tumour. Nonetheless there were only 129 new cases of lung cancer out of 10,061 over a period of 3.7 years. The effect was only seen in lung cancer and not non-lung cancer. Plausibility is added though by the apparent dose-effect relationship, arguably stronger than the dose-effect relationship on recurrent cardiovascular events.

Genetic variation and so-called Mendelian randomisation are experiments of nature that can give some insight into causality. In the context of variation over the IL-1 gene locus there have been a number of case association studies that indicate some, variable effect on cancer. A particular issue in this context is obtaining haplotypes that are both informative and exactly mirror the effect of the agent—in this case IL-1 beta inhibition. Unfortunately, the biggest such genetic study from the IL-1 genetics consortium (12) identifies a haplotype that more exactly mirrors anakinra (IL-1 receptor antagonist) and whilst this eliminates IL-1 beta signalling it also inhibits IL-1 alpha. In addition, genetic studies will impact on life-long risk, which may impact on tumour formation as well as presentation, the latter more likely to be affected by a short-term treatment of the type used in Cantos. Nonetheless this study, which incidentally reported IL-1 inhibitory haplotypes as increasing coronary risk (the opposite of the main Cantos study) in the supplementary data file shows effects of IL-1 inhibition on cancer cases. This study showed IL-1 inhibition to accentuate breast and renal cell cancer but there was a non-significant effect reducing lung cancer. It would seem that these genetic studies do not confirm or refute the lung cancer findings of Cantos but they might imply that there are specific cancer subtypes that are

mutable by IL-1 inhibition rather than a generalizable effect in accord with the Cantos cancer observations.

Biologically, can we expect IL-1 beta inhibition to reduce tumour presentation? The pathophysiological basis of lung cancer is well beyond this article but it is clear that tumorigenesis requires a number of genetic hits and these somatic mutations increasingly determine classification and may in due course drive specific treatment. Inflammation, however, is a common association in cancer with causal implications. It appears that immune cells are a substantial proportion of cells in the tumour microenvironment. Tumour associated macrophages (TAMs) form a significant proportion of these and are probably bone marrow derived. TAMs have a powerful effect on tumour growth and anti-inflammatory gene deletion of macrophages facilitates tumour growth. TAMs are likely to be key mediators of tumour vasculogenesis. Whilst macrophages can be tumour initiating, it is likely that their main roles in cancer are tumour progression and spread (4) IL-1 could be a mediator at a number of these steps but data is lacking and, therefore, the evidence for a central role in these processes is not strong. Evidence of an effect of IL-1 beta on implanted cancer growth has, however, been gathered from animal models but brings with it all the limitations of those types of experiments.

Immunological intervention in cancer is, however, an area of considerable interest and some promise. Research focused on the provision of either active or passive immunity to target tumours through immunotherapy are underway. Therapies may be categorized broadly upon mechanism of action and, although not universally successful, examples exist of phase II and III studies devised to provide immunity through: cancer vaccine therapy [phase III: belagenpumatucel-L (13), talactoferrin (14), BEC2/BCG (15), racotumomab (16)]; the adoptive transfer of immune cells [phase III: lymphocyte-activated killer cell (17)]; administration of checkpoint inhibitors [phase II: ipilimumab (18)]; or the targeting or administration of cytokines [phase III: IL-2 (19)]. Importantly, what separates these studies from CANTOS is the patient cohort—the majority of cancer therapeutic studies enroll patients with an established diagnosis of cancer whereas CANTOS demonstrated a post-hoc reduction in lung cancer presentations in a previously undiagnosed cohort.

So where does this leave us? The data from CANTOS on the effect of canakinumab cannot be dismissed—it is certainly a level above birth star signs! The background plausibility is, however, not overwhelming, certainly from

the human. As is so often concluded in this situation—more data are needed.

What is really needed is that we move forward with big trials in such a way that more data of real fidelity are generated from the word go. An adaptive trial design that allows examination of cardiovascular endpoints as well as cancer outcome, although probably larger and more expensive, would seem to be the way forward in this field and probably in many others. In the meantime, additional experimental cell biology will help.

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). AR 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.

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Cite this article as: Crossman D, Rothman AM. Interleukin-1 beta inhibition with canakinumab and reducing lung cancer—subset analysis of the canakinumab anti-inflammatory thrombosis outcome study trial (CANTOS). *J Thorac Dis* 2018;10(Suppl 26):S3084-S3087. doi: 10.21037/jtd.2018.07.50