A cardiovascular trial discovers the potential therapeutic efficacy of interleukin-1β inhibition in lung cancer

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Over the last two decades, a wealth of experimental and clinical data have intimately linked dysregulated production of the potent pro-inflammatory cytokine interleukin (IL)-1β with numerous chronic inflammatory and autoimmune diseases, among which the best documented include rheumatoid arthritis (RA) and cardiovascular disease (e.g. atherosclerosis).[1-3] Notably, these disease associations have provided the impetus to develop clinical grade inhibitors against IL-1β or its receptor, with the IL-1 receptor antagonist anakinra being the first such inhibitor approved in 2001 for clinical use.[3]

Despite its promise, short-comings of anakinra include its short half-life, thus requiring daily high dose injections, and a lack of specificity for IL-1β due to its blockade also of IL-1α signalling.[3] Accordingly, the marketplace has since seen the advent of the human anti-IL-1β monoclonal antibody, canakinumab,[4,5] which due to its high specificity and longer half-life has demonstrated marked clinical benefits when used at comparatively lower doses and less frequently in a diverse array of inflammatory and autoimmune disease states.[4-7] Now, in this issue of *The Lancet*, Ridker and colleagues report findings from the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), a large, randomized double-blind trial designed to evaluate the efficacy of canakinumab in atherosclerosis patients who were free of previously diagnosed cancer and displayed persistent systemic inflammation.[8] However, in a surprising twist, 3-monthly canakinumab treatment led to a significant dose-dependent reduction in total cancer mortality over 3-5 years follow-up. Maximal benefit was observed for canakinumab at the highest 300mg dose compared to placebo (hazard ratio 0.49 [95% CI 0.31-0.75]; p=0.0009), and coincided with a substantial drop in incidence rates of 0.64 (placebo) to 0.31 (300mg canakinumab) per 100 person-years. Moreover, these observations with 300mg canakinumab were primarily due to reductions in lung cancer mortality (hazard ratio 0.33 [95% CI 0.18-0.59]; p=0.0001) and incidence rates (0.49 versus 0.16 per 100 person-years).[8]

At first glance, the biased effect of canakinumab on lung cancer is intriguing since lung cancer is among many epithelial cancers associated with chronic inflammation.[9] In support, trial

participants with elevated median baseline levels of inflammatory biomarkers high sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 were more prone to be diagnosed with lung cancer, and canakinumab dose-dependently reduced systemic hsCRP and IL-6 levels.[8] However, considering that 70.7% of CANTOS participants were current or past smokers, it might be expected that canakinumab would exhibit a preferential effect on lung cancer because tobacco smoke causes pulmonary inflammation and is the major lung cancer risk factor.[9]

From an oncology viewpoint, the study design of CANTOS, as expected, has numerous limitations, and thus interpretation of findings which are largely preliminary should be taken with caution. A key question that arises is whether the effect of canakinumab on lung cancer is restricted to individuals with pre-existing atherosclerosis, and how does their smoking status influence potential responsiveness? Also, without any genetic and molecular subtyping of lung cancers in the CANTOS trial, it is unclear how the data as presented could inform the use of anti-IL-1β therapy in precision medicine, which is an area of great need in (lung) cancer.

Despite these concerns, the CANTOS data on lung cancer does make an important and timely contribution to the paucity of literature on the role of IL-1β in lung cancer. Indirect evidence linking IL-1β with lung cancer could be extrapolated from experimental data associating IL-1β with chronic obstructive pulmonary disease (COPD), a known risk factor for lung cancer.[10,11] However, in the CANTOS trial canakinumab had no impact on the incidence of COPD cases,[8] which is supported by previous trials using canakinumab (ClinicalTrials.gov identifier, NCT00581945) and MEDI8968, a human anti-IL-1 receptor monoclonal antibody, which similarly did not provide any clinical benefit to COPD patients.[12] Collectively, these data suggest a potential disconnect in the pathological role of IL-1β in the lung, where it may play a more prominent role in the progression and metastasis of lung cancer, as noted by Ridker *et al*,[8] rather than lung inflammation *per se* (in the context of COPD).

In summary, while the CANTOS trial findings are unlikely to directly inform treatment in lung cancer, they do nonetheless shed light on IL-1β as a potential therapeutic target in lung cancer,

which alone warrants further investigational studies to be undertaken on the role of IL-1β in this malignancy. Moreover, the CANTOS findings should now be exploited to refine the design of future clinical trials using canakinumab with a specific focus on lung cancer, which by including important clinicopathological information such as tumour histological type and TNM staging, along with molecular/genetic profiling of tumours, will assist patient stratification for targeted IL-1β therapy.

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