Editorial

Anti-inflammatory therapy with canakinumab for atherosclerotic disease: lessons from the CANTOS trial

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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.* CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377:1119-31.

Submitted Jan 05, 2018. Accepted for publication Jan 15, 2018.
doi: 10.21037/jtd.2018.01.119
View this article at: http://dx.doi.org/10.21037/jtd.2018.01.119

Inflammation plays a pivotal role in the development of atherosclerosis and in plaque instability (1). This has led to the hope that agents inhibiting inflammatory pathways in atherosclerosis can be employed to improve the clinical outcome of patients with coronary disease over and above treatments that target cholesterol accumulation and platelet initiated thrombosis (2).

Unfortunately, progress in translating this hope to clinical reality has until recently proved frustrating. Non-steroidal anti-inflammatory drugs (NSAIDs) proved to have adverse effects on cardiovascular outcomes (3). Inhibition of Phospholipase A2 proved ineffective (4). Inferences from experience with disease modifying biological anti-rheumatic drugs (DMARDs) including TNFα, IL-6 and IL-1 also failed to demonstrate any clear benefit on cardiovascular outcomes and systematic literature reviews confirmed that they may increase the risk of infection (5). Experience with TNFα inhibition in heart failure had adverse effects and inhibition of IL6 with tocilizumab and in patients with rheumatoid arthritis failed to show any cardiovascular benefits over TNFα inhibition with etanercept (6). Anakinra which targets the IL-1 receptor has been shown to have an effect on hs-CRP levels but its effects on clinical outcomes has not been evaluated (7).

With this background, the results of the CANTOS trial which examined the use of canakinumab in patients with a history of acute coronary syndromes (8), has been widely welcomed as it offers hope that targeting inflammation indeed may be of benefit in patients with established coronary disease.

Canakinumab is a human monoclonal anti-human IL-1β antibody. IL-1 is a pivotal cytokine in the inflammatory cascade upstream from IL6, TNFα and CRP. IL-1β is the circulating form of IL-1 produced as a precursor (pro-IL-1β) that is activated following activation of the NLRP3 (previously termed NALP3) inflammasome (9). The central role of the inflammasome in gout has long been recognized and recognition that it is also activated by cholesterol crystals provide a potential link between cholesterol deposits in the vascular bed and the inflammatory process evident in atherosclerosis (10).

In Europe, canakinumab is approved for the treatment of several rare periodic fever syndromes, active systemic juvenile rheumatoid arthritis and acute gout. In the US the FDA approved its use for periodic fever and juvenile rheumatoid but rejected its use for gout citing insufficient data and safety concerns related to risk of infection (11).

The ability of canakinumab to reduce inflammatory markers without any effect on lipid levels or platelet function, made it an ideal agent to test the independent benefit of inflammatory therapy in patients with atherosclerosis.

In the CANTOS trial, 10,061 patients with previous myocardial infarction and a hs-CRP level of >2 mg/L

were randomised to receive 3-monthly SC injections of one of canakinumab at either 50 mg, 150 mg, 300 mg, or placebo (8). The primary efficacy outcome was the composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. The secondary outcome was the composite of the primary outcome and urgent revascularization, an important and valid outcome measure in trials designed to evaluate therapies that prevent progression of atherosclerosis.

At a median follow up of 3.7 years, the hazard ratios for the primary outcome were 0.93 [95% confidence interval (CI), 0.80 to 1.07] in the 50-mg group, 0.85 (95% CI, 0.74 to 0.98; P=0.021) in the 150-mg group, and 0.86 (95% CI, 0.75 to 0.99; P=0.031) in the 300-mg group.

After adjustment for the comparisons of multiples dose levels, only the 150-mg dose met the pre-specified threshold for statistical significance for both the primary and secondary outcomes.

Canakinumab was associated with a small but statistically significant risk of fatal infection (0.31 *vs.* 0.18 events per 100 person-years; P=0.02) and it had no effect on all-cause mortality. Of interest, a pre-specified analysis demonstrated a reduction in the incidence of lung cancer in the pooled canakinumab population (P=0.0001 for trend across groups), and a reduction in lung cancer related mortality (P=0.0002) (12). Evidence that the results were due to modulation of inflammation was strengthened by a pre-specified analysis showing that the benefits in the trial were confined to those who achieved an on-treatment reduction of hs-CRP below 2 mg/L (13).

Despite excitement with the overall result, CANTOS has met with a mixed reception (14) for several reasons including the relatively underwhelming overall effect on the primary outcome, the lack of a clear dose response, the higher rates of infection and the significant risk of fatal infection, the need to administer a monoclonal antibody by injection, and its estimated total annual cost of almost $US200,000 per year (15). Taken together it would appear most unlikely that canakinumab will be widely used for the prevention of recurrent coronary syndromes.

Despite this, the CANTOS trial can be acknowledged as a truly landmark trial as it was a bold achievement in translating state of the art biology to the bed side to examine the true importance of inhibiting IL1β in patients with stable coronary disease. The results of the trial will therefore act as a strong stimulus to trial other safer, more widely available, less expensive therapies capable of inhibiting the IL pathway in patients with coronary disease over decades.

Although there are several potential candidates for this role, the only anti-inflammatory agents currently undergoing phase III trials in patients with coronary disease are methotrexate and colchicine (16-18).

Methotrexate has effects on a number of cytokines other than IL-1 that may be relevant to inflammation in atherosclerosis and meta-analyses of retrospective cohort studies in patients with rheumatoid arthritis suggest it may have cardiovascular benefits compared with other DMARDs (19). This has been the impetus for the Cardiovascular Inflammation Reduction Trial (CIRT) examining the cardiovascular effects of methotrexate in patients with stable coronary disease in the hope that at low dose it will prove effective without the toxicity and high risk of discontinuation reported with its use in patients with rheumatoid arthritis (20).

Colchicine is widely used for secondary prevention of gout, and has FDA approval for life time therapy at doses up to 2.4 mg daily in patients with Familial Mediterranean Fever (21). In contrast to canakinumab which targets a single anti-inflammatory pathway in an otherwise complex disease, colchicine is an agent with multiple targets. Specifically, it has the unique ability to dampen the activity of the full palette of cellular players including neutrophils, macrophages, mast cells and T-cells that mediate inflammatory injury in atherosclerotic plaque. In addition, it has effects on endothelial and platelet-function and can dampen the growth of vascular smooth muscle cells, fibrocytes and osteophytes that become activated in the healing response to vascular injury (22). In patients with coronary disease colchicine 0.5 mg daily reliably reduces hs-CRP over and above statins (23), has favourable effects on coronary atherosclerotic plaque (24) and has been demonstrated to reduce cardiovascular events (25). Importantly no concerns have been raised about long-term tolerance or safety in patients with FMF or cardiovascular disease (26). The promise of low dose colchicine in patients with coronary disease is being explored in two trials. The LoDoCo2 study is designed to determine its effects in ~5,000 patients with stable coronary disease (17) and the COLPOT study of similar size, is examining its effects in patients with recent acute coronary syndromes (18).

The CANTOS study of canakinumab in survivors of myocardial infarction provided important proof that the IL-1 pathway is an integral contributor to the instability of atherosclerotic plaque. In addition, it provides sound evidence that inhibiting the IL-1 pathway has the potential

to improve the outcome of patients with established coronary atherosclerosis. The challenge now is to find drugs which can achieve this at acceptable cost and with low risk of side effects so that patients can be treated for their disease over decades.

Acknowledgements

The LoDoCo2 trial is funded by the National Health and Medical Research Council (NHMRC) of Australia.

Footnote

Conflicts of Interest: Drs. Thompson and Nidorf are Principal Investigators of *The LoDoCo2 Trial*: *Low Dose Colchicine for secondary prevention of cardiovascular disease*. ACTRN12614000093684.

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Cite this article as: Thompson PL, Nidorf SM. Anti-inflammatory therapy with canakinumab for atherosclerotic disease: lessons from the CANTOS trial. J Thorac Dis 2018;10(2):695-698. doi: 10.21037/jtd.2018.01.119

