CANTOS – is selective targeting of inflammation in atherosclerosis enough?

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Title Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial

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Journal *Lancet* 2018; 391: 319–28.

Financial and Competing Interests: No conflict of interests declared

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Summary

Cardiovascular disease (CVD), including ischemic heart disease, is a major cause of morbidity and mortality the world over, as reaffirmed in the recent Global Burden of Disease study.[1] This is in spite of advances in the medical management of such diseases, including the use of antiplatelet agents and statins. A large proportion of CVD is due to atherosclerosis.[2] Inflammation plays a major role in atherosclerosis, from initiation up to the terminal events of plaque rupture and thrombosis.[3] Macrophages not only play a role in the formation of foam cells in the atherosclerotic plaque, but also secrete inflammatory cytokines, such as interleukin 1 beta (IL-1β), via activation of intrinsic mechanisms including the inflammasome. IL-1β, in turn, drives further downstream inflammatory processes, including the secretion of the potent inflammatory cytokine interleukin 6 (IL-6). Considering the inflammatory basis of atherosclerosis, IL-1β is an attractive target to test the role of blocking inflammation in impeding atherosclerosis.

Canakinumab is a fully human monoclonal antibody against IL-1β, administered monthly by subcutaneous injection. A recent clinical trial, the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), studied the role of canakinumab at doses of 50, 150 and 300 mg, compared to placebo, in patients with established ischemic heart disease who continued to have elevation of high sensitivity C-reactive protein (hsCRP) in serum beyond 2 mg/l. The primary endpoint was the incidence of nonfatal myocardial infarction or ischemic stroke or death related to cardiovascular events, with the reported secondary endpoint being the primary endpoint with the additional requirement for an urgent revascularisation procedure. The study involved over 10,000 patients, approximately 6,700 were split into roughly equal groups, and each group received one of the three dose amounts of canakinumab with the rest receiving placebo. Statistical analysis revealed that the incidence rates of the primary and secondary endpoints at nearly 4 years of follow up were significantly lower for the group receiving 150 mg canakinumab than those receiving placebo. Overall, the use of canakinumab conferred greater risk of developing fatal infections, but the overall mortality rate remained similar in all groups. These findings were in spite of the fact that levels of lipids remained similar before and after drug administration.[4] A recently published secondary analysis of CANTOS further attempted to stratify patients based on whether they could attain a level of hsCRP <2 mg/dl a month after the first dose of canakinumab (3,484 patients) and compared the risk of attaining the primary endpoints to those who could not do so (2,868 patients). Intriguingly, those who could attain a hsCRP level <2 mg/l had a significantly lower risk of recurrence of cardiovascular events, by 25%, than those who could not, and a significant reduction in both cardiovascular mortality and all-cause mortality, by 31%, respectively, irrespective of the dose of canakinumab used.[5]

Opinion

Literature on the use of canakinumab in patients with atherosclerosis has emerged over the years. In a study of 556 patients with diabetes mellitus and high risk of cardiovascular events, administration of canakinumab at doses ranging from 5 to 150 mg monthly had beneficial

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effects on reduction of hsCRP, IL-6 and fibrinogen when compared to placebo, despite a lack of a significant effect on haemoglobin A1c, blood sugars and lipids.[6] Another study failed to demonstrate a reduction in atherosclerotic burden assessed using mean carotid wall area and aortic elasticity at 12 months in patients with either overt diabetes mellitus or impaired glucose tolerance treated with canakinumab (150 mg monthly) compared to placebo, despite significant reductions in hsCRP and lipoprotein a levels.[7] However, another secondary analysis from CANTOS demonstrated a significant reduction in incident cardiovascular events with canakinumab in patients with chronic kidney disease (and consequently, a higher risk of cardiovascular disease) when compared to placebo.[8] Another interesting finding of CANTOS was the reduction in total cancer risk, incident lung cancer and risk of mortality due to lung cancer with canakinumab when compared to placebo, especially in those receiving a monthly dose of 300 mg canakinumab.[9]

The findings of CANTOS challenge conventional management strategies for CVD. First, it must be emphasised that the included subjects had already been on optimum secondary prevention strategies for coronary artery disease, including antiplatelet agents and statins. Second, the possibility of identifying a group that may have a greater potential for benefit by measuring hsCRP levels 1 month after first administration of canakinumab has important public health implications. Should such directly targeted anti-inflammatory therapies for secondary prevention become widespread, the costs for healthcare providers could be minimised by further continuing their administration only in those in whom it is effective in reducing the levels of hsCRP below 2 mg/dl. It may be useful to also investigate such personalised medicine strategies in the context of other directly acting anti-inflammatory agents in CVD.

Since IL-6 is another important inflammatory cytokine driving atherosclerosis,[3] partly driven by IL-1β and, therefore, influenced by canakinumab,[6] studies have also looked at the role of blocking IL-6 in atherosclerosis. In a group of patients with rheumatoid arthritis at high risk of cardiovascular events, treatment with tocilizumab, a monoclonal antibody to IL-6, improved endothelial function over 16 weeks, but the same was not seen with treatment with either anti-tumour necrosis alpha agents or conventional disease-modifying agents.[10] A study attempting to look at reductions in recurrence of CVD at 30 days in patients receiving tocilizumab 162 mg compared to placebo could not meet targets for recruitment, and was, therefore, halted prematurely after recruiting only 28 patients in whom there was no difference with tocilizumab when compared to placebo.[11] Beneficial reductions in cardiovascular outcomes in patients with rheumatic diseases treated with immunosuppressive agents, some of them by actions on the atherosclerotic plaque, holds promise for further exploration of immunomodulatory therapies in patients with CVD.[12] A greater challenge is the identification of those patients who may benefit from such strategies to optimise their use, a future towards which CANTOS has shown a direction.

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