CANTOS
A Gigantic Proof-of-Concept Trial

Borja Ibañez, Valentin Fuster

Cumulative evidence links inflammation with atherothrombotic disease. Conversely, the role of modulating the inflammatory process as a therapeutic target has remain an unproven hypothesis until the execution of the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study). On the one hand, this trial provides robust evidence that interleukin-1β (IL-1β) inhibition by canakinumab reduces the incidence of repetitive atherothrombotic events in patients with postmyocardial infarction already on state-of-the-art treatment but with a residual inflammatory risk. On the other hand, the absolute antiatherothrombotic effect size of this intervention seems small (189 patients had to be intervened during 1 year to prevent 1 myocardial infarction episode) and associated with a mild increase in the incidence of serious adverse events (≈1 in 750 patients intervened during 1 year developed a fatal infection or sepsis). Beyond all these considerations, CANTOS represents a gigantic (10 000 patients) proof-of-concept trial.

Atherosclerosis is a systemic disease with a long clinically silent phase. Arterial wall lipid deposition, the hallmark of atherosclerosis, begins early in life. Atherosclerotic plaques grow gradually for several years, the disease becoming clinically overt only when the plaque is large enough to restrict blood flow or becomes unstable and ruptures, causing a thrombus. From its earliest asymptomatic phase through to the late clinical manifest stages, atherosclerosis is predominantly an inflammatory disease, featuring leukocyte activation, cytokine release, and infiltration by eosinophils, neutrophils, and macrophages. Epidemiological studies have revealed that circulating inflammatory biomarkers, especially C-reactive protein (CRP) measured by a high sensitivity (hs) assay, are associated with a higher incidence of atherothrombotic events (myocardial infarction, stroke, etc.).[1] All these observations suggested that strategies to reduce inflammation would lead to a reduction in atherothrombotic events. However, it is important to note that the evidence linking inflammation to atherosclerosis is associative, and evidence for a causal role of inflammation in atherothrombotic events or even plaque progression remains elusive. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) provided only indirect evidence, showing that rosuvastatin therapy reduced the incidence of cardiovascular events in asymptomatic individuals with normal low-density lipoprotein (LDL) cholesterol levels but elevated hsCRP.[2] Rosuvastatin therapy reduced hsCRP, and the degree of this reduction was associated with a higher protective effect. However, the concomitant reduction of LDL made it difficult to conclude that the reduction in cardiovascular outcomes was because of inhibition of inflammation and not simply an LDL-driven effect in a high-risk population (identified by the inflammatory biomarker hsCRP). Further indirect evidence linking inflammation reduction to atherothrombotic protection came from the reduced cardiovascular event rates among patients with rheumatoid or psoriatic arthritis treated with the anti-inflammatory drug methotrexate.[3,4]

IL-1β is upstream CRP in the inflammatory cascade. IL-1β is activated by the NLRP3 (NOD-like receptor P3) inflammasome in the cell and released into the circulation.[5] There is strong experimental evidence for a direct involvement in atherothrombosis of IL-1β.[5] Moreover, human atherosclerotic plaques contain higher IL-1β concentrations than nonatherosclerotic vascular regions.[6] IL-1β is the target of the human monoclonal antibody canakinumab, approved for the treatment of rheumatological disorders. Canakinumab has been shown to reduce markers of inflammation in diabetic patients with atherosclerotic disease.[7] The apparently direct role of IL-1β in atherothrombosis and the availability of a clinically approved specific inhibitor set the basis for the CANTOS trial. CANTOS was designed as a definitive proof-of-concept of the inflammatory theory of atherothrombosis. The trial studied ≈10 000 patients with a history of myocardial infarction and an hsCRP ≥2 mg/L and who were optimally treated according to current standards (including statin therapy in >90% of the trial population).[8] Study participants were randomized to receive placebo or 1 of 3 canakinumab doses (50, 150, 300 mg), administered subcutaneously every 3 months for ≈4 years. Baseline LDL cholesterol levels were low (≈80 mg/dL) in all groups and did not change during the trial span. After 4 years of follow-up, the primary end point (a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) was significantly lower in the 150 mg canakinumab group versus placebo. The 300 mg dose had a similar numeric effect, but the multiple statistical comparisons yielded a nonsignificant difference versus placebo. The hazard ratio for the incidence of the primary outcome for the 150 mg canakinumab dose versus placebo was 0.85; however, this corresponded to a modest absolute risk reduction: to avoid 1 primary end point event, 156 patients have to be treated with canakinumab during 1 year. The

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reduction in the primary outcome was mainly driven by a reduction in myocardial infarction; stroke and cardiovascular mortality did not differ between groups.

Of intriguing interest, cancer mortality (all cancers and lung cancer specifically) was significantly lower in the pooled canakinumab group than in the placebo group. Incident lung cancer was significantly less frequent in the 150 and 300 mg groups versus placebo.[9]

A particularly important outcome was the result of the prespecified analysis of the primary outcome in canakinumab-treated patients according to their biological response, evaluated as the reduction in hsCRP at 3 months. Patients with an on-treatment hsCRP level below the median (1.8 mg/L) had a highly significantly lower rate of atherothrombotic events and a hazard ratio for the incidence of the primary outcome of 0.73.

The results of CANTOS trial constitute a great scientific advance in the field of atherothrombosis, by confirming a theory proposed several decades ago. CANTOS has demonstrated beyond doubt that inflammation plays a role in the development of atherothrombosis and, more importantly, that it can be effectively modulated. This trial shows that the residual risk in patients with low LDL levels can be partially mitigated by inhibiting the IL-1β inflammatory pathway. However, from the clinical point of view, the net clinical benefit of canakinumab is less easy to determine. On the one hand, the relative beneficial effect of canakinimab on atherothrombotic events is robust despite the only primary end point component significantly reduced was myocardial infarction. On the other hand, the magnitude of the effect was modest: 189 patients have to be treated with canakinumab 150 mg during 1 year to prevent 1 myocardial infarction event. Moreover, the CANTOS publications do not report details of myocardial infarctions (eg, with or without ST-segment elevation, degree of necrosis, spontaneous or periprocedural etc.). This information is important for evaluating the clinical benefit of a therapy in which the primary end point reduction was mainly driven by a reduction in myocardial infarction.

Recent European Society of Cardiology Guidelines for the treatment of patients with ST-segment–elevation myocardial infarction recommend the use of additional lipid-lowering therapies (ezetimibe or evolocumab) in patients with postmyocardial infarction who do not reach the LDL goal of 70 mg/dL despite maximum tolerated statins.[10] This new recommendation is based on the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)[11] and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International)[12] trials. In the FOURIER trial, LDL cholesterol levels in evolocumab-treated patients was 30 mg/dL while in the IMPROVE-IT trial, LDL cholesterol levels in ezetimibe-treated patients was 54 mg/dL. These LDL cholesterol levels were reached without a significant increase in serious side effects. In both trials, the incidence of myocardial infarction and stroke was significantly reduced by the active treatments. It is currently unknown how aggressive LDL-lowering treatment according to new guidelines (eventually with statins plus additional lipid-lowering therapy) affects the residual inflammatory risk[13] and magnitude of effect of canakinumab.

It is also important to remember that the benefit of canakinumab in reducing atherothrombotic events is not a free lunch, and there are potentially serious side effects. The most worrisome outcome is the significantly higher death rate from infection in patients who received canakinumab than in those receiving placebo.[8] Nonetheless, fatal infection or sepsis incidence during follow-up was low: >750 patients had to be exposed to canakinumab during 1 year to induce one of these serious events. In general, according to the trial data, it can be expected that ≈1 in 360 patients receiving canakinumab during 1 year will develop any infection.

Decisions on whether to incorporate canakinumab into the pharmacological armamentarium for the treatment of postmyocardial infarction need to consider all the questions raised here. There is little possibility of another large trial in this patient population in the near future. The CANTOS study design had to be changed because of financial considerations, and the original sample of 17 200 patients was cut to 10 000. The investigators extended follow-up to allow accumulation of the preplanned number of events. This change in no way affects the results reported but highlights the difficulty of repeating such a large trial. The CANTOS results, therefore, provide the only evidence available to regulators and the scientific community in deciding whether canakinumab should be approved for this indication. Another aspect that should be incorporated in the equation is the anticipated high cost of this new therapy. Current cost of canakinumab for approved indications is ≈$16 000 per 150 mg injection ($64 000 year cost according to CANTOS treatment regime). This hypothetical cost seems to exceed generally accepted net cost-effectiveness thresholds, estimated to be far below $10 000 per year for this type of postmyocardial infarction population already treated according to state-of-the art therapy.[14]

Given the role of inflammation in atherosclerosis initiation and progression, the antiatherothrombotic effect of canakinumab might be vastly greater if this therapy was initiated at the asymptomatic stages, in a population with identified subclinical disease.[15] However, this potential benefit might be accompanied by an increased and prolonged vulnerability to infection. The enormous benefits to be obtained by preventing the first atherothrombotic event could even partially mitigate the anticipated high costs of this therapy.

Today, our view is that canakinumab is unlikely to be suitable for all patients with postmyocardial infarction but may be considered as treatment for a specific patient subset: postmyocardial infarction patients with high hsCRP levels despite optimal LDL cholesterol–lowering therapy according to current guidelines, and be maintained after 3 months only in patients with a significant hsCRP drop at this time point. In patients receiving canakinumab for this indication, special attention should be payed to leukocyte counts and signs of infection. In the meantime, as clinical scientists we are satisfied by the robust confirmation of the inflammatory hypothesis in atherothrombosis provided by CANTOS, a gigantic trial according to the proof-of-concept standards.

Disclosures

None.

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