Inflammation Revisited: Atherosclerosis in The Post-CANTOS Era

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Abstract

It is fairly well accepted in the scientific community that atherosclerosis carries features of a local and low-grade systemic inflammation. However, it was unclear thus far whether this is simply an epiphenomenon or if it plays a causal role in atherosclerosis and its clinical complications. After several failed attempts, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) has provided convincing evidence of interleukin-1 beta as a target whose neutralisation by a selective antibody reduces major cardiovascular events without affecting LDL-cholesterol. This provides strong evidence in support of the inflammation hypothesis and will certainly stimulate research in this area and open the way for novel therapy in high-risk patients following MI.

Keywords

Inflammation, atherosclerosis, biomarkers, outcome studies, canakinumab

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The notion that atherosclerosis carries features of an inflammatory disease has existed for quite some time. As early as 1856, Rudolf Virchow in his Textbook on Pathology mentioned the term "coronaritis". Almost 150 years later, following the elucidation of major cardiovascular risk factors in the 1950s Framingham Study, Russell Ross entitled his 1999 review on mechanisms of atherosclerosis "*Atherosclerosis – an inflammatory disease*".[1] An abundance of data, including experimental studies in vascular biology and extensive observational research in the general population and clinical cohorts, have demonstrated a strong association between elevated markers of inflammation and short- and long-term cardiovascular outcomes. These include various acute phase reactants, in particular C-reactive protein (CRP), and various cytokines. Nevertheless, inflammation has continued to be considered as an epiphenomenon and not suitable as a target for intervention.[2]

Substantial progress in the treatment of atherosclerotic complications – in particular in secondary prevention – has led to a significant reduction of recurrent cardiovascular events. This has been through the use of polypharmacotherapeutic strategies including potent lipid-lowering drugs such as statins, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, along with the introduction of early percutaneous coronary intervention in acute coronary syndrome (ACS) with consecutive application of dual antiplatelet therapy. Despite such progress, several registries over the last 10 years have clearly demonstrated that there is still considerable risk in patients after MI. For example, data from the Global Registry of Acute Coronary Events (GRACE)[3] have shown that approximately 20 % of patients following an ACS have died after 5 years. Further evidence from the large Swedish National Registry in more than 100,000 patients has suggested that after 1-year post-ACS, approximately 15–20 % of patients have experienced an event, in particular cardiovascular death, MI or stroke.[4] Finally, the most recent Second Manifestations Of Arterial Disease (SMART) registry of more than 6,000 patients with manifest vascular disease showed that approximately 40 % of patients had a 10–20 % risk for recurrent events over 10 years, which was highest in those with multi-vessel disease, even after optimised treatment of all known risk factors.[5] This raises the question of the existence of other pathophysiological pathways, and inflammation may be considered one of them.

With the introduction of proprotein convertase subtilisin-kexin type 9 (PCSK9) antibodies, unprecedented low LDL-cholesterol levels have been shown to be achievable. For example, the Further Cardiovascular Outcomes Research With PCSK9 Inhibition In Subjects With Elevated Risk (FOURIER)[6] study reported levels of 30 mg/dL and the Global Assessment Of Plaque Regression With A PCSK9 Antibody As Measured By Intravascular Ultrasound (GLAGOV)[7] study reported levels in the region of 36 mg/dL. Despite this, a significant number of patients continue to go on to have a recurrent event or show progression in intravascular ultrasound studies.

During recent years we have seen the failure of a number of clinical trials that aimed, at least in part, to target inflammation. For example the Stabilization of Atherosclerotic Plaque By Initiation Of Darapladib Therapy (STABILITY)[8] and Stabilization Of Plaques Using Darapladib-Thrombolysis In Myocardial Infarction 52 (SOLID-TIMI-52)[9] trials investigated the effect of the lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor darapladib. While they showed no signal of harm, they were neutral in their effect regarding main cardiovascular outcomes. Lp-PLA2 is a molecule that generates free fatty acids and phosphatidylcholine from oxidised LDL in the vessel wall. Its selective inhibitor, darapladib, has been shown to both decrease systemic levels of Lp-PLA2 and to decrease Lp-PLA2 expression in plaque. A further phospholipase inhibitor targeting secretary phospholipase

A2, varespladib, was tested in the Evaluation Of Safety And Efficacy Of Short-Term A-002 Treatment In Subjects With Acute Coronary Syndrome (VISTA-16)[10] study, which even showed increased morbidity and mortality in the intervention group. Furthermore, losmapimod, a drug that has been suggested to decrease oxidative stress in the vascular wall, has failed in the Phase 3 Clinical Outcomes Study To Compare The Incidence Of Major Adverse Cardiovascular Events In Subjects Presenting With Acute Coronary Syndrome Treated With Losmapimod Compared To Placebo (LATITUDE-TIMI 60)[11] trial. What all these targets have in common is that they are not on the interleukin (IL)-6 signaling pathway. This may be important, because inflammation is a complex and fairly redundant system that on the one hand is needed for reparative processes and on the other hand may exert negative effects through its prolonged activation. It has been shown convincingly in several Mendelian randomisation studies that IL-6 most likely is on the causal pathway in atherogenesis, and variants associated with impaired function of the IL-6 receptor have been associated not only with decreased surrogate parameters like CRP but also with decreased incidence of CHD events.[12,13] Thus, similar to lowering of LDL cholesterol for which the LDL receptor is crucial, it may be that interfering with inflammation is not always beneficial but has to rely on specific pathways.

A few years ago the Low-Dose Colchicine (LoDoCo) trial,[14] a small study comprising only 532 patients, reported dramatic reductions of recurrent cardiovascular events in stable CHD patients receiving 0.5 mg colchicine/day over 3 years. Colchicine has been known in clinical medicine for many years and is mainly used to treat acute gout, but more recently has also been introduced in cardiovascular medicine to reduce inflammatory reactions of pericarditis and Dressler's syndrome. Colchicine has been known to act, at least in part, via inhibition of IL-6.

Based on convincing experimental studies in vascular biology along with clinical data,[15] IL-1 beta has been suggested to play a central role in the inflammation cascade. Therefore, a few years ago, the protocol of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) study was conceived.

The highlight of this year's European Society of Cardiology congress in Barcelona was indeed the presentation of the eagerly awaited results from the CANTOS trial.[16] CANTOS was a randomised double-blind trial of canakinumab, a fully human monoclonal antibody that selectively inhibits IL-1 beta and leaves the IL-1 alpha pathway intact. The trial included 10,061 patients with a previous MI and elevated CRP (≥2 mg/L) measured by a high-sensitivity (hs) assay as the major entry criteria. This intervention was compared with placebo on top of standard of care, which included among others adequate treatment of blood pressure and high-dose statin therapy resulting in a baseline LDL-cholesterol of 82 mg/dL. Randomised patients represented a high-risk group particularly characterised by a median hs CRP of 4.1 mg/L. The incidence rate for cardiovascular disease outcomes in the placebo group was 2 times higher compared with all-comers after MI in contemporary studies. Furthermore, approximately 40 % of patients had diabetes, 25 % were ongoing smokers and the majority (4/5) had already undergone prior revascularisation. Canakinumab administered at 50, 150 or 300 mg subcutaneously every 3 months resulted in dose-dependent reduction in surrogate inflammatory endpoints such as (hs) CRP and IL-6. There was no interference with lipid metabolism: LDL cholesterol was not affected at all, whereas only a slight increase in triglycerides was observed. The main clinical outcome was a primary endpoint consisting of non-fatal MI and non-fatal stroke or cardiovascular death, which was reduced by 15 % with the 150-mg dose and equally so with the 300-mg dose. The secondary endpoint, which additionally included urgent revascularisation, showed an even stronger effect – a 17 % relative risk reduction over a median follow-up of 3.7 years. Most importantly, the effect on cardiovascular endpoints was strongest in those who were identified as responders based on the fact that their achieved CRP during the study would be below the median hs CRP in the overall population. In this group the relative risk reduction amounted to 27 %. In addition to these clinically relevant reductions in cardiovascular outcomes, incidence rates of other pro-inflammatory diseases such as arthritis, osteoarthritis, and gout were also significantly reduced. Further analyses of CANTOS in the future will reveal whether or not other diseases associated with an inflammatory response, such as diabetes, supraventricular arrhythmias, deep vein thrombosis, pulmonary embolism or incident heart failure after the index event can also be reduced. A further interesting observation in CANTOS, based on exploratory analyses, showed a marked reduction in cancer mortality, in incident lung cancers and in particular in fatal lung cancers.[17] For example, the 300-mg dose of canakinumab led to a 51 % reduction in cancer mortality, with regard to incident lung cancer there was a 67 % reduction and, finally, a 70 % reduction in fatal lung cancers was observed. These findings are not surprising based on the pathophysiology of IL-1 beta, whereby convincing data also demonstrate that it is intimately involved in tumourigenesis, tumour invasiveness, and metastasis formation of various cancers, in particular lung cancers, but also for example colon cancer.[18] This clearly represents an important additional clinical benefit of canakinumab and is also theoretically important since it demonstrates that, despite an intervention in the immune system by application of canakinumab over 3.7 years, the immune system does not seem to be compromised. Otherwise one would have expected an opposite effect, namely increased morbidity and mortality from malignancies.

Overall, CANTOS has changed the clinical landscape in cardiovascular medicine and it has now become quite clear that inflammation can no longer be considered simply as an epiphenomenon but that it represents a new treatment strategy to further reduce residual risk in patients after a cardiovascular event. After many years of extremely controversial debate, this trial demonstrates a paradigm shift in our understanding of the pathophysiology of atherosclerosis. ■

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