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Atherosclerosis as an inflammatory disease: Doubts? No more

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Atherosclerosis is the pathological hallmark of the majority of cardiovascular disease (CVD), such as myocardial infarction and ischemic stroke and a multifactorial event that has being debated for decades in term of causes and triggers. First hints about an inflammatory cause of atherosclerosis came from the pioneering work of Russell Ross lab (reviewed and summarized in [1]), that highlighted its pathogenic mechanism as an initial vascular response to endothelial injury which, in turn, triggers a local chronic inflammatory self-maintaining response [1–3].

Further research demonstrated that the inflammatory component of atherosclerosis represented by various cells and mediators of the immune system is an important factor in disease progression and plaque rupture [4–7] as it is known the majority, but not all CVD patients with atherosclerosis background have a relevant inflammatory imprinting [8]. Accordingly, results from the JUPITER trial demonstrated that, among patients with a heightened level of high-sensitivity C-reactive protein (CRP), a nonspecific inflammatory marker, high dose statin use determined a lower risk of cardiovascular events than control [9]. However, as the level of low density lipoprotein (LDL) cholesterol were lowered from baseline in these statin-treated patients, it was impossible to conclude that alteration of the inflammatory *milieu* was the reason for the clinical. Thus, it seems that it has long been suspected that patients with high levels of CRP and other inflammatory markers are at increased risk of adverse CVD events, but the scientific community has struggled to translate this knowledge into new treatment regimens.

Now it has been finally shown that a specific anti-inflammatory molecule can protect against triggering events (such as plaque rupture for example) in heart attack survivors who remain at risk of further vascular events despite well-controlled lipid blood amounts. This molecule is an antibody that binds interleukin (IL)-1β (canakinumab). In the CANTOS trial (more than 10,000 patients), recently published in NEJM [10] canakinumab lowered the incidence of heart attack, stroke and death by 15%. When compared to placebo canakinumab reduced the high sensitivity CRP protein level in a dose-dependent fashion in few months and which were maintained so during dosing time interval, with no reduction in the LDL cholesterol level [10].

By blocking IL-1β — the main circulating form of IL-1 — canakinumab blocks this pivotal mediator of inflammation [11] which is produced when cholesterol crystals activate the NLRP3 inflammasome as well as when oxidized LDL are produced locally, likely with the contribution of other pathological mechanisms [6,12–14].

IL-1β then induces expression cascade of several pro-inflammatory molecules, such as IL-6 [15], a cytokine that triggers production of CRP and that has been implicated directly in atherosclerotic development and plaque rupture [16].

What we gather from this study that likely represents an important milestone in atherosclerosis and cardiovascular disease research?

Firstly we have to highlight and acknowledge the definitive proof of the inflammatory hypothesis in atherosclerosis pathogenesis and its natural history in a clinical setting: this knowledge potentially opens to a plethora of a new clinical research era that can modify further the outcome of these still deadly disease.

Noteworthy, IL1 activity is not easy measurable and the choice to use CRP as a biomarker of IL1 activity is far from perfection: changes in CRP could be a good marker of response, but baseline levels could be misleading and behave as a bad predictor of a given response (with obvious consequences to future studies design and stratification).

Secondly, in regard to the efficacy of this new treatment we have to consider that the cardiovascular risk reduction in the CANTOS trial mirrors the advantage that has been reached using PCSK9 inhibitors [17] and, more broadly, highlights the significance of controlling cardiovascular risk by targeting inflammatory pathways (IL1 is likely not the

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only pro-inflammatory molecule involved in determining cardiovascular risk).

Thirdly, the cost of such a therapy should also be considered: canakimumab is an expensive drug approved for rare autoimmune diseases and one injection costs more than US $16,000 (150 mg in 1 ml of subcutaneous solution is USD 16770, from https://www.drugs.com/price-guide/ilaris, accessed March 8th, 2018). It was used every three months in the CANTOS trial: maintaining the current price, it would be roughly US $67,000 for a year of therapy. The manufacturer probably needs to lower the price as a preventive cardiovascular drug (it is a viable option, owing to the larger market share available in the cardiovascular setting).

Finally it is worth noting that the high costs and the slightly higher risk of infection found in the treated population make canakinumab an unlikely candidate in a cardiovascular setting at the moment, but at the same time it opens the doors to less expensive and other more generic drugs that could be tested in the anti-inflammatory settings (such as metothrexate, see [18]).

Of note, in the CANTOS trial cancer mortality was significantly decreased in patients receiving canakinumab versus patients receiving placebo, specifically in regard to lung cancer incidence and mortality [19], supporting the role of inflammatory milieu and specifically of the IL1 pathway in tumor biology and human cancerogenesis [20].

Further studies need to be performed to better delineate the role of canakinumab as an effective cardiovascular drug (and to better delineate its potential role in the intriguing clinical oncology setting), but the milestone achieved is nevertheless significant: atherosclerosis is an inflammatory disease and this proven mechanism could change therapy guidelines and ultimately outcomes in the next few decades. This is, indeed, an innovation for the Scientific Community and the patients.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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