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Editorial commentary: Are cytokines ready for prime time? Insights from markers and trials

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Cardiovascular (CV) disease remains a leading source of morbidity and mortality worldwide. Over recent decades, it has become apparent that clinical risk factors alone do not neatly capture the individual risk profile for future CV events. This unmet need has created an impetus for the discovery of biomarkers reflective of the underlying disease pathophysiology that can provide a personalized approach to risk stratification and risk modification. An additional value of biomarker discovery is that they do not just track a response to therapy but can potentially suggest novel therapeutic targets.

Activation of the immune system has emerged as an important player in atherosclerosis and cardiac remodeling post-acute myocardial infarction (AMI). Additionally, inflammatory markers are elevated in all phenotypes and stages of heart failure, albeit it remains unclear whether this relationship is causal [1]. As similar pathways are activated in autoimmune diseases, there has been a proliferation of studies translating anti-inflammatory therapies into use for treatment of CV diseases. The timely review by Hartman et al focuses on cytokines, inflammatory mediators that have a broad signaling footprint involving both the innate and adaptive branches of the immune system as well as interstitial cells in the arterial wall and myocardium [2]. For ease of discussion, we will separate the current medical knowledge into three main domains of pathophysiology.

Treating the plaque

In 1997, Ridker and others demonstrated that in apparently asymptomatic healthy individuals baseline CRP elevation correlated with an increased CV risk, raising the hypothesis that anti-inflammatory agents may be beneficial in CV disease [3]. Two decades later, the CANTOS trial directly tested the causation between CV disease and inflammation [2,4]. However, the important message of the trial is not contained in the modest treatment benefit observed with canakinumab, with number needed to treat of 189 to prevent 1 AMI over 1-year period, with no mortality benefit and unclear definition of AMI that drove the significant difference in the results. Rather, there is a subgroup that exhibited responsiveness

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to the treatment achieving CRP levels < 2 mg/L, and those were the patients who derived the greatest benefit of the therapy, including a 31% reduction in mortality [5]. Compared to the responder group, the non-responders showed no treatment benefit.

The CANTOS trial suggests a paradigm shift in how we deliver therapy to our patients—from a treat-all strategy to using a personalized approach where one identifies responders prior to treating with expensive therapies with all the incumbent side effects (infections in the case of canakinumab). CANTOS, thus, is teaching us that there are likely many unmeasured variables such as genetic, epigenetic and environmental factors that alter the individual's responsiveness to a tested therapy. Instead of dismissing the oftentimes negative results of clinical studies with anti-inflammatory agents, we could focus efforts on finding reliable biomarkers that will allow to carefully phenotype patients and tailor therapies to those subgroups that derive true benefit.

Reducing size of infarction

Inflammation is an integral component of tissue healing post-AMI and consists of two phases. There is an initial robust inflammatory reaction with infiltration of the injured area by neutrophils, Ly6^{high} monocytes, NK cells and T lymphocytes leading to secretion of IL-1 β , TNF- α and IFN- γ . A few days following the acute insult, the reparative phase of MI begins. During that phase, the immune cell types above revert to an anti-inflammatory phenotype accompanied by the secretion of anti-inflammatory and pro-fibrotic cytokines such as monocyte-derived IL-10 and TGF- β .

All of the studies in Hartman's review have employed cytokine inhibition therapies delivered at the time of reperfusion and extending for at most 2 weeks post AMI [2]. In the AMI literature there is a notable lack of studies that have addressed the potential inflammatory dysregulation in the second healing phase of AMI. Many of the cited trials by Hartman et al. have used as end-points imaging indices of myocardial remodeling such as end-systolic and end-diastolic left ventricular volumes (LVESV and LVEDV) [2]. LV remodeling, however, is the long-term response of the myocardium to the initial insult. Tipping the inflammatory balance toward a heightened level of inflammation during the reparative phase could be a culprit for adverse myocardial changes. This has been suggested in a study that has demonstrated that in STEMI patients elevated levels of IL-1 β 2 months post PCI predicted LVESV and LVEDV indices at 1 year [6]. Thus, the question remains if our timing is right in delivering anti-inflammatory therapies post AMI.

In the studies cited by Hartman et al., measured levels of circulating cytokines have been used as markers to monitor treatment response [2]. However, unlike laboratory models where genetic background, size of insult and intervention timing are controlled for, in human trials such uniformity is not the case. It is unknown how different cytokine levels in patients with AMI reflect the size of the pathological insult. Studies have shown that genetic polymorphisms affect levels of circulating cytokines thus confounding their use as uniform markers of injury extent [7]. Additionally, the immune system has built-in redundancies as well as pleiotropic downstream effects making inhibition of one branch of its network to be a too narrow of a therapeutic target. Potentially addressing other components of the injury

response such as mitochondrial dysfunction and endothelial health together with the inflammatory response could be a better approach in targeting post-AMI adverse myocardial remodeling.

Treating heart failure

Measurement of inflammatory biomarkers both in animal models as well as in patients with heart failure (HF) has consistently shown a pro-inflammatory profile with elevated levels of multiple cytokines, including IL-1, IL-6, TNFR1 and others [1]. However, it is still elusive if this relationship is causative or associative ubiquitously across HF etiologies. The challenge of studying inflammation in HF is that oftentimes the diagnosis is established later in the disease course and downstream of the initial precipitant. However, Hartman et al. have omitted an important at-risk population for HF from causes with proven inflammatory origin, namely the post heart transplant population. One in eight heart transplant recipients dies from HF due to progressive cardiac allograft vasculopathy (CAV) [8]. CAV is an accelerated fibroproliferative disease affecting the vasculature mediated by immune cell activation and secretion of numerous cytokines, including IL 1, 2, 4, 5, 6, IFN- γ , TNF- α [8]. mTOR inhibitors have been shown to slow down CAV progression and reduce mortality by blocking several signal transduction pathways in both T and B cells leading to impaired proliferative response to cytokines and growth factors [8].

Additionally, it has been demonstrated that in brain dead donors, which constitute the largest pool of cardiac organ donation, there is a strong immune system activation leading to a pro-inflammatory milieu in the transplanted allograft. Complement activation has been identified as a major player promoting inflammatory cell migration, cytokine release and adaptive immune modulation, and has been confirmed in heart recipients from brain dead donors [9]. Atkinson et al. have demonstrated in a murine model that treatment with a targeted complement inhibitor significantly improved graft survival and inflammatory mediators [9]. Therefore, the OHT literature can provide guidance in the use of anti-inflammatory therapies in the broader context of versatile heart failure phenotypes.

Future directions

Despite the challenge in translating positive findings with anti-inflammatory therapies from animal models to humans, the current landscape of immunomodulatory therapies in heart disease has highlighted the need for reliable and robust biomarkers that reflect the health of the myocardium or vasculature. Only by understanding end organ remodeling at a cellular level will we be able to carefully phenotype subgroups of patients who are most likely to respond to a given therapy, and thus expand the cardiac indications of anti-inflammatory therapies. Although the inflammatory cascade mediators appear to be attractive biomarkers, most lack stability and most importantly they lack specificity for myocardium and cardiac vessels. Anti-inflammatory therapies may be successfully tracked once basic research efforts identify cardiomyocyte, smooth muscle, fibroblast and endothelial cell derived biomarkers that specifically identify the different anatomical and cellular domains of the heart.

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