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Review

Unmet needs in the management of atherosclerotic cardiovascular disease: Is there a role for emerging anti-inflammatory interventions?

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ABSTRACT

Atherosclerotic cardiovascular disease is the leading cause of death worldwide. Despite extraordinary advances in the understanding of the pathophysiology and the utilization of very effective medications such as statins, there still remains a significant residual risk. In fact, even after optimal interventional and medical therapy, the possibility of recurrent myocardial infarction remains at approximately one third for five years after acute coronary syndromes, thus emphasizing the urgent need for novel therapies to prevent the progress of atherosclerosis. In addition, over the past two decades, although atherosclerosis has been clearly identified as an inflammatory disease of the arterial wall from compelling data of animal and human studies, clinical applications related to this accumulated knowledge are scarce. This review presents a brief description of the role of inflammation in atherogenesis, and examines selected potential anti-inflammatory interventions that are being tested in ongoing clinical trials which have been designed to prevent adverse cardiovascular events as well as provide a proof of concept regarding the inflammatory hypothesis of atherosclerosis.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in most countries. Despite being a multifactorial disease, compelling evidence from epidemiological and clinical studies and experiments in animal models have established that elevated concentrations of cholesterol, mainly transported by low-density lipoprotein (LDL) particles, promote atherosclerotic lesions. Although statin-based lipid-lowering therapies have been shown to reduce major cardiovascular (CV) events, even after strong reduction in LDL-cholesterol (LDL-C) levels, there is still a significant residual risk that cannot be ignored. Despite continuous advances in the treatment of acute and/or chronic coronary syndrome with catheter- and pharmacotherapy-based interventions, additional therapies are still needed to reduce the rate of recurrent CV events, which remains quite undoubtedly high [1,2].

2. Role of inflammation in atherosclerosis

Atherosclerosis is a complex disease of the arterial wall characterized by the formation of lesions (atheromas or atherosclerotic plaques which lead to progressive occlusion of arteries) at susceptible points of the arterial tree. These lesions remain silent for decades, but over time, they may cause stenosis or rupture. This can lead to distal ischemia and thrombosis, with clinical consequences, such as myocardial infarction (MI), stroke, and a wide variety of other clinical implications.

For many years, atherosclerosis was considered a degenerative disease caused by the continuous accumulation of cholesterol in the arterial intima. Furthermore, the idea that atherosclerosis is a predominantly lipid-driven disease has dominated the field of CV diseases. Over the past two decades, however, the concept of atherogenesis has changed due to new evidence that atherosclerosis is predominantly a chronic low-grade inflammatory disease of the vessel wall. In fact, the involvement of inflammation in the pathogenesis of atherosclerosis has been

Abbreviations: ACS, acute coronary syndrome; ASCVD, Atherosclerotic Cardiovascular Disease; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention primary prevention; CAD, coronary artery disease; CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CARE, Cholesterol and Recurrent Events; CI, confidence interval; CIRT, Cardiovascular Inflammation Reduction Trial; CRP, C-reactive protein; CV, cardiovascular; hs-CRP, high- sensitivity CRP; IFN-γ, interferon gamma; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; JUPITER, Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; MTX, methotrexate; NSTEMI, non-ST elevation myocardial infarction; NLRP3, NOD-like receptor, pyrin domain containing-3; OxLDL, oxidized LDL; PROVE IT–TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22; REVERSAL, Reversal of Atherosclerosis with Aggressive Lipid Lowering; SNPs, single-nucleotide polymorphisms; STEMI, ST-segment elevation acute myocardial infarction; TnT, troponin T; TNF-α, tumor necrosis factor alpha.

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suspected since the 19th century, based on pathological observations made by the pioneers Rudolf Virchow, Karl Rokitansky, and others [3]. Moreover, the concept that inflammation may play an important role in atherosclerosis is one that has grown in parallel with the pathology itself for more than a century. Nevertheless, it is only in recent years that chronic inflammation has become recognized as a contributory factor in the development of ASCVD and other diverse chronic diseases, with new evidence continually being added that supports atherosclerosis being an inflammatory condition.

It is important to consider that while the purpose of an inflammatory process is the resolution of injury, pathogens, or infections by initiating an appropriate necessary wound healing response, chronic inflammation, in fact, represents a deviation from a natural biologic or physiologic response to an abnormal pathologic process. Thus, ASCVD is an inflammatory condition characterized by quantitative and qualitative lipoprotein abnormalities and a "maladaptive" inflammatory response. In contrast with acute inflammatory events which are typically self-limiting, atherosclerosis is an "unresolved inflammatory condition" lacking the typical resolution phase, as characterized by a change from pro-inflammatory to anti-inflammatory mediators and finally tissue regeneration [4].

In atherosclerosis, inflammation starts and evolves in response to cholesterol accumulation in the arterial intima of the large and medium arteries. However, new insights into innate immunity have altered the understanding of the events that initiate and drive the inflammation, thereby changing several concepts regarding the pathogenesis of the inflammatory disorders and making it clear that innate and adaptive immune responses play a pivotal role throughout the initiation, progression, and clinical consequences of atherosclerotic diseases. In fact, one of the initial stages involves endothelial cell activation and recruitment of inflammatory cells to the vessel wall, leading to a wide array of monocyte-derived macrophages, T cells, mast cells, dendritic cells, etc., within the atherosclerotic lesions [5–7]. Moreover, it is important to note that structural alterations, in particular the exposure of proteoglycans, facilitate the retention of LDL particles in the intima, where they are susceptible to oxidative modification by reactive oxygen species (ROS) and enzymes released from inflammatory cells, making these lipoproteins more pro-inflammatory and enhancing the activation of the endothelium [8]. However, not only monocytes but also different types of leukocytes adhere and roll on the activated endothelium overlying the retained lipids, facilitated by adhesion molecules, before migrating into the arterial intima and producing pro-inflammatory cytokines or chemokines [9].

Monocyte-derived macrophages take up the oxidized LDL (OxLDL) via scavenger receptors, leading to the formation of lipid-laden foam cells. The process continues with permanent accumulation of lipids, inducing endoplasmic reticulum stress and triggering foam cell apoptosis [10].

Finally, atherosclerotic plaques may suddenly rupture and induce coronary thrombosis, presenting an acute coronary syndrome (ACS). The notable features of unstable rupture-prone plaques are infiltration of several inflammatory cells, a large lipid core, and a thin fibrous cap [11,12]. In addition, immunity features – cell mediated and humoral – are involved in the development of atherosclerotic lesions. T lymphocytes, mainly CD4+ Th1 T-cell subtype, are seen in the atherosclerotic plaques, with OxLDL particles appearing to be the mediators of T-cell activation within the plaques. Activated CD4+ T lymphocytes in turn contribute to plaque instability by releasing tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ), among other pro-inflammatory cytokines [13].

Recently, another factor within atherosclerotic plaques, the cholesterol crystal, has been identified as the predominant endogenous danger signal that initiates an inflammatory response via stimulation of the caspase-1-activating NOD-like receptor, pyrin domain containing-3 (NLRP3) inflammasome [14]. Due to retention of lipoproteins in the vessel wall, cholesterol accumulation may result in the formation of cholesterol crystals, which are taken up by macrophages and elicit an inflammatory reaction through the activation of NLRP3 inflammasome, thus leading to an amplifying cascade of immune responses. Therefore, cholesterol crystals may be an initiating and/or an exacerbating factor in atherosclerosis by inducing cell injury and apoptosis [14].

The major function of NLRP3 is to sense phagocytosed material and relay the signal to caspase-1, resulting in proteolytic cleavage and secretion of (pro-interleukin) IL-1β as bioactive IL-1β and IL-18, ultimately leading to increased production of other downstream inflammatory cytokines [15]. IL-1β and IL-6, among other systemic inflammatory mediators such as TNF-α, are released into the circulation leading to hepatic production of C-reactive protein (CRP) [16,17]. The NLRP3 inflammasome has now emerged as a cross-link between inflammation and cholesterol metabolism in atherosclerosis [18,19]. Thus, cholesterol crystals might lead to damage of foam cells and the lipid-rich necrotic cores characteristic of vulnerable atherosclerotic lesions, resulting in volume expansion and/or rupture of the plaques.

3. Unresolved dilemma: is inflammation an "efficient cause" of atherosclerosis?

The ancient Greek philosopher Aristotle describes and argues for the four causes needed to explain any material change in the world, with "efficient cause" being the source of the primary principle of change. Bearing this in mind, is it possible to extrapolate this principle by affirming that inflammation can be considered the cause rather than an accompanying consequence of atherogenesis?

Despite compelling data from studies in animals and humans, the final confirmation of the inflammatory hypothesis of atherosclerosis has remained elusive. Serum biomarkers of inflammation, such as high-sensitivity CRP (hs-CRP), were shown to independently predict the risk of CV disease in observational studies [20]. This evidence was first presented by Ridker et al. in apparently healthy men in 1997, and subsequently confirmed in healthy women [21]. In several meta-analyses, CRP has been shown to be as relevant to vascular risk prediction as either total or HDL-cholesterol, with hs-CRP being stable and easy to use in clinical practice [22]. At present, more than 60 prospective cohort studies have confirmed that a variety of inflammatory biomarkers, such as CRP, IL-6, TNF-α, P-selectin, serum amyloid A, fibrinogen, and adhesion molecules, are all associated with future CV risk in otherwise healthy individuals [23]. Among these biomarkers, hs-CRP is now considered the standard for CV risk prediction due to the robust clinical data, its abundance, and a magnitude of risk prediction that can be compared with the increase in cholesterol or blood pressure [22]. In fact, the mechanistic role of CRP in plaque deposition is extremely complex and possibly exerts its pro-atherogenic effects in several cells involved in atherogenesis [24,25]. For example, CRP plays a key role in the early stages of the atherosclerotic process by facilitation of monocyte adhesion and transmigration into the blood vessel wall [26], whereas in vitro studies have also shown associations among CRP, inhibition of endothelial nitric oxide synthase, and impaired vasodilation. However, despite the involvement of CRP in the atherosclerotic process having been strongly suggested, there is still no conclusive clinical evidence showing a functional role of this biomarker in ASCVD.

On the other hand, treatment with statins reduces the levels of both LDL-C and CRP along with a concurrent reduction in the number of CV events. The first evidence for this came from an investigation named the CARE (Cholesterol and Recurrent Events) study, a secondary prevention trial in patients with previous MI, in which pravastatin reduced hs-CRP levels independent of the magnitude of LDL-C reduction [27]. In a post hoc analysis of the (AFCAPS/TexCAPS) (Air Force/Texas Coronary Atherosclerosis Prevention primary prevention) study, subjects with LDL-C < 149 mg/dL and hs-CRP > 1.6 mg/L had a 42% statistically significant relative risk reduction with lovastatin compared with placebo. In contrast, subjects with LDL-C < 149 mg/dL and hs-CRP < 1.6 mg/L had a very low event rate and showed no benefits with lovastatin compared