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.

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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
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 progression, and clinical consequences of atherosclerotic diseases. In fact, an increasing number 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 cellular infiltration as either total or HDL-cholesterol, with hs-CRP being stable and predictive of an increased risk of vascular events [27]. In clinical data, its abundance, and a magnitude of risk prediction that can be compared with the increase in cholesterol or blood pressure [22]. 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 facilitating 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 AFCAST/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 with placebo.
with placebo. A group of individuals more responsive to lipid-lowering therapy was identified from their high hs-CRP levels [28]. Related to this, the role of hs-CRP in CV disease prevention became more clearly identified after the JUPITER (Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study results were published in 2008 [29]. The JUPITER trial randomized 17,802 middle-aged men and women with low-to-intermediate risk and LDL-C and hs-CRP levels < 130 mg/dL and > 2 mg/L, respectively, to rosuvastatin 20 mg and placebo. The trial was prematurely discontinued due to a very significant (44%) relative risk reduction (95% confidence interval [CI], 46%–69%; P < 0.00001) in the primary endpoint, a composite of MI, stroke, revascularization, hospitalization for unstable angina, or death from CV causes. Moreover, the LDL-C and hs-CRP levels were found to be reduced by 50% and 37%, respectively, in the rosuvastatin arm. In the JUPITER study, the degree of CRP lowering following rosuvastatin therapy was also found to predict the therapeutic benefit of the intervention independent of the lipid-lowering effect [29,30]. Moreover, a pre-specified analysis showed that the lowest number of CV events was observed in those who achieved both very low LDL-C (<70 mg/dL) and low hs-CRP (<1 mg/L) levels.

Similarly, in two secondary prevention trials, PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) [31] and REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) [32], sub studies related to inflammation showed that intensive therapy with atorvastatin 80 mg compared with pravastatin 40 mg achieved a greater reduction not only in LDL-C levels but also in hs-CRP levels, with both being associated with an important reduction in clinical events and a slower progression of atherosclerotic lesions. Likewise, subjects with LDL-C < 70 mg/dL and hs-CRP < 1 mg/L on atorvastatin had the lowest rate of major adverse cardiovascular events (MACE). In the same way, the addition of the cholesterol absorption inhibitor, ezetimibe to statins further reduces LDL-C and hs-CRP.

Recently, in the IMPROVE-IT trial, the relationship between both achieved LDL-C and hs-CRP targets (dual target) and the primary end point –CV death, major coronary event, or stroke- was analyzed for patients randomly assigned to simvastatin monotherapy or a combination of simvastatin/ezetimibe. In the 15,179 patients studied, simvastatin plus ezetimibe significantly increased the likelihood of meeting the prespecified targets of LDL-C < 70 mg/dL and hs-CRP < 2 mg/L, one month after randomization. Those achieving these dual targets (39%) had lower primary end point rates than those (14%) meeting neither target (38.9% versus 28.0%; adjusted hazard ratio, 0.73; 0.66–0.81; P < 0.001) [33]. Here, the attainment of both goals was associated with significantly improved CV outcomes in comparison with those meeting neither target after multivariable adjustment.

The investigators also pointed out that, although the addition of ezetimibe increased the likelihood of target achievement, the specific choice of agent used to reach the target did not have any influence on the outcome [33]. Interestingly, this approach seemed to work well even at low LDL-C levels in this study, where a significant number of patients had LDL-C levels < 50 mg/dL. Thus, when the authors applied a lower exploratory target of LDL-C < 50 mg/dL and hs-CRP < 1 mg/L, the rates of the primary end point were decreased in all subgroups compared with the already above-mentioned subgroups defined by the higher targets.

Therefore, a fundamental question remains about whether or not inflammation plays a significant role in patients who achieve very low LDL-C levels such as 30 mg/dL or even less when, for example, treated with PCSK9 inhibitors. Furthermore, such potent interventions for LDL lowering –which are currently being tested in extensive clinical programs including nearly 70,000 individuals worldwide– have to date been unable to significantly reduce hsCRP levels.

The association between elevated hs-CRP levels and ASCVD is well established, but there is inconclusive evidence that reducing hs-CRP levels alone will prevent MACE. On the other hand, subjects with LDL-C levels < 130 mg/dL will most likely reap a net benefit from statin therapy, with or without elevated hs-CRP levels. Yet, even for this very well documented and studied inflammatory marker CRP, causality is still heavily debated [23]. Related to this, the relevant issue in fact should not be about targeting CRP per se but about targeting inflammatory mechanisms with the objective of treating and preventing ASCVD, with Mendelian randomization studies potentially being able to help address this controversy. By focusing on single-nucleotide polymorphisms (SNPs) in the CRP gene associated with elevated CRP levels, it was shown that lifelong exposure to increased CRP levels were not linked with CV risk elevation [34,35]. Nevertheless, two other Mendelian randomization studies have demonstrated that the genetic polymorphism associated with decreased IL-6 signaling was correlated to lower lifelong CRP levels, with a concomitant reduction in CV risk [36,37]. Although these studies do not prove a causal relationship between inflammation and vascular events, they support the idea that targeting the IL-6 pathway may be a valid strategy for preventing CV events.

4. Targeting inflammation in atherosclerotic cardiovascular disease

Despite the success of statins in the JUPITER study in reducing both inflammation and LDL-C levels and consequently MACE, the major issue of targeting inflammation remains unresolved. Independent of its LDL-lowering capacity, statins have also been shown to attenuate inflammation [38,39], but the following questions still remain: what was the contribution of decreasing CRP to the primary endpoint? Were the very encouraging results of JUPITER just linked to LDL-C reduction? Answers to these questions might come from testing the inflammatory hypothesis of atherosclerosis, without reducing LDL-C levels and directly randomizing patients to be targeted for anti-inflammatory therapies. CRP is produced in the liver, stimulated by IL-1α, TNF-α, and IL-6. Basic animal experiments have indicated that interfering with such cytokines and chemokines is an emerging approach for anti-inflammatory therapy that could reduce atherosclerosis [40,41]. Of the various pathways and inflammatory mediators that have been implicated in atherogenesis, cytokine IL-1 in the innate inflammatory response is considered to be a “master cytokine” in the local and systemic inflammations and seems to play a central role in the atherosclerotic process [42]. Furthermore, blocking IL-1 activity has revealed a pathological role of this cytokine in a broad spectrum of diseases, including type 2 diabetes and heart failure [43,44].

The structurally related polypeptides IL-1α, IL-1β, and the IL-1 receptor antagonist (IL-1Ra) are relevant constituents of the IL-1 family and are predominantly synthesized by mononuclear phagocytes, smooth muscle cells, and endothelial cells, in response to microbial stimulus or endogenous triggers such as uric acid or cholesterol crystals [45]. While IL-1α is present in the cells of healthy individuals and its precursor is active, IL-1β is absent and its precursor needs to be activated, requiring intracellular cleavage by caspase-1, which in turn requires activation from a complex of intracellular proteins called the inflammasome, as described above. Both IL-1α and IL-1β activate the IL-1 type 1 receptor, and IL-1Ra competitively inhibits their binding.

In fact, the balance between IL-1 and IL-1Ra plays a vital role in the potential development of several inflammatory diseases [46]. Treatment with a recombinant form of the naturally occurring IL-1Ra, anakinra, which blocks both IL-1α and IL-1β, safely resolves or can significantly improve the inflammatory disease state [47]. For example, in a pilot study including patients with ST-segment elevation acute myocardial infarction (STEMI), IL-1 blockade with anakinra was shown to be safe and favorably affected left ventricle remodeling after MI [48]. Two other pilot double-blinded studies of IL-1 blockade for two weeks in STEMI patients have been shown to reduce acute inflammatory response after three months of follow-up, whereas in a median follow-up of 28 months in 40 patients, treatment with anakinra was associated with a hazard ratio of 1.08 (95% CI, 0.31–3.74; P = 0.90) for the...
combined endpoint of death, recurrent acute MI, unstable angina pectoris, or stroke, and with a hazard ratio of 0.16 (95% CI, 0.03–0.76; \( P = 0.008 \)) for death or heart failure. Therefore, it was concluded that 14 days of treatment with anakinra has a neutral effect on recurrent ischemic events, and may lead to a long-term reduction in new-onset heart failure after STEMI [49].

Another pro-inflammatory upstream cytokine, IL-6, has been targeted in several studies. IL-6 is secreted by macrophages in atherosclerotic plaques as a response to specific antigens and has been shown to contribute to the progression and instability of the atherosclerotic plaque. In addition, smooth muscle cells in the tunica media of blood vessels and adipocytes can also produce IL-6. This multifunction cytokine, responsible for stimulating acute-phase protein synthesis, has also been associated with a poor outcome in ACS [50].

Recently, an interesting study with tocilizumab, a humanized anti-human IL-6 receptor antibody, was presented by Kleveland et al. [51] during the 2015 ESC Congress in London. Overall, 117 patients with acute non-ST elevation myocardial infarction (NSTEMI) were randomized to receive a single dose of tocilizumab or placebo at a median of 2 (0–12) days after MI onset, and hs-CRP and troponin T (TnT) levels were measured at different time points. The area under the curve (AUC) for hs-CRP was 55% lower in the active treatment group (\( P = 0.009 \)), and the absolute changes in hs-CRP and TnT levels from baseline were consistently lower in tocilizumab treated patients throughout all measurements. In addition, there was a significant correlation between hs-CRP and TnT levels in both treatment groups, with favorable effects observed in terms of attenuation of the inflammatory response and troponin release in patients with NSTEMI treated with the anti-IL-6 receptor monoclonal antibody. However, since tocilizumab increases LDL-cholesterol levels, and is therefore not a pure anti-inflammatory effect, future studies on this agent should be more focused on CV safety than efficacy [52].

In humans, classical risk factors, such as hyperlipidemia, diabetes mellitus, smoking or hypertension, and circulating levels of IL-1β have been associated with coronary artery disease (CAD) along with higher concentrations of IL-1β and IL-1Ra in atherosclerotic coronary arteries compared with normal arteries [53,54]. Similarly, NLRP3 and downstream cytokine (IL-1β and IL-18) levels were linked with severity of CAD, and a dynamic variation was also seen in patients with acute MI. A gradual increase in plasma levels of IL-1β and IL-18 was associated with increasing CAD severity. These results revealed that the increased expression of NLRP3 and downstream cytokines might reflect CAD severity [55].

Currently used immune modulator drugs, such as methotrexate (MTX), which directly targets the inflammatory process of atherogenesis, are widely available. Observational studies in patients with rheumatoid arthritis (RA) corroborated this favorable impact of immunosuppression by demonstrating that MTX not only attenuated systemic inflammation but additionally decreased CV events [56]. Moreover, a systematic review of the effect of MTX on CV disease in patients with RA concluded that its use was associated with reduced risk of CV events, suggesting that MTX improves comitant atherosclerosis in such patients [57]. Finally, in a recent meta-analysis authored by Micha et al., MTX was associated with a 21% lower risk for total CV disease (\( n = 10 \) studies; 95% CI, 0.73–0.87; \( P < 0.001 \)) and an 18% lower risk for MI (\( n = 5 \); 95% CI, 0.71–0.98, \( P = 0.01 \)), suggesting that a direct treatment of inflammation may reduce the risk of CV disease [58].

Two major clinical studies based specifically on both approaches will test this hypothesis and are currently in progress using MTX [59] and the IL-1β inhibitor canakinumab [60]. The study using MTX was initiated by the National Heart Lung and Blood Institute with the acronym CIRT (Cardiovascular Inflammation Reduction Trial) in patients with chronic atherosclerosis and either diabetes mellitus or metabolic syndrome, who are being randomized to low-dose MTX, 15–20 mg/week or placebo. This low-dose MTX is a generic anti-inflammatory drug widely used for the treatment of RA. The trial is on-going and approximately 7000 patients will be included. The primary endpoint is the reduction of major CV events and the results can be expected in 2018.

CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) is the first large, randomized, controlled, clinical study testing whether the use of canakinumab, a fully human anti-IL-1β monoclonal antibody, can prevent secondary CV events in subjects with prior MI and considered to be at high risk due to elevated levels of hs-CRP despite undergoing the usual therapy including statins. The enrollment period has now been completed, with 10,065 subjects included. The results of the CANTOS trial are expected in 2017 (Fig. 1).

Multiple studies support the rationale for specifically targeting IL-1β, because IL-1β may participate in host defense, and in an elegant review Dinarello et al. have extensively analyzed this issue [43]. Although IL-1β is secreted from cells at one site, it can affect tissues at a different or even distant site, whereas IL-1α acts locally. Thus, IL-1β secreted by the adipose tissue could affect pancreatic insulin-producing cells in patients with diabetes. In addition, monocytes from patients with diverse autoimmune-inflammatory diseases release more IL-1β than the corresponding cells from unaffected individuals. Neutralizing IL-1β antibodies have been shown to prolong drug efficacy by several weeks after cessation of therapy, consequently implying that only a low dose is required to treat an IL-1β-mediated disease in several cases, with a long half-life being an emerging and optimal strategy for chronic diseases, such as type 2 diabetes or ASCVD [45].

Another classic anti-inflammatory drug, colchicine, which is used to treat gout, is also being tested for CV protection. In addition to its known anti-inflammatory properties, recently a newly discovered interesting mechanism has been described, since colchicine appears to block the crystal-induced activation of the NLRP3 inflammasome, thereby decreasing secretion of the pro-inflammatory cytokines IL-1β and IL-18 [61]. In the LoDoCo study, 532 patients with stable CAD received 0.5 mg/day of colchicine or non-placebo control treatment. As was anticipated, more than 20% of those treated with colchicine experienced adverse gastrointestinal side effects leading to the medication being stopped, but interestingly, the active intervention significantly reduced the primary endpoint of recurrent ACS, cardiac arrest or non-embolic stroke (HR: 0.33, 95% CI: 0.18–0.59, \( P = 0.001 \)) [62].

Similarly, in a recent systematic review and meta-analysis, in 5 trials including 1301 patients at risk for CV disease (CAD, ACS or stroke, postangioplasty, or congestive heart failure), colchicine reduced composite CV outcomes by ~60% (risk ratio 0.44, 95% CI: 0.28–0.69, \( P = 0.0004 \)); and showed a trend towards lower all-cause mortality (risk ratio 0.50, 95% CI 0.23–1.08, \( P = 0.08 \)) [63]. These data support the need for
large-scale randomized controlled trials of colchicine for secondary prevention of ASCVD.

5. Concluding remarks

In addition to the current LDL-lowering therapies, extensive research is still required on the role of anti-inflammatory and/or immune-modulating drugs in targeting the inflammatory component of atherogenesis. To date, the strategy of using inflammatory modulation for the prevention and treatment of ASCVD remains unproven.

There is growing evidence of different pro-inflammatory pathways being involved in the atherosclerotic process. Thus, taking into account the role of IL-1β in atherosclerosis, as discussed in this review, the principle of applying anti-IL-1 therapy to reduce CV risk is a matter of crucial interest, which promises to provide important future benefits in the treatment of ASCVD.

Two large-scale clinical trials based on this approach are presently underway. In CIRT, low-dose MXT is being used as a broad-spectrum upstream anti-inflammatory therapy; and in the CANTOS study, the selective IL-1β monoclonal antibody canakinumab is targeted toward vascular inflammation. Both studies are expected to provide critical findings to help reduce the rates of recurrent MI, stroke, and CV death among stable CAD patients who remain at risk due to a persistent pro-inflammatory response.

As neither of these anti-inflammatory interventions seems to have a great impact on plasma lipid levels, this makes these approaches more promising for testing the pure inflammatory hypothesis than other significantly different emerging treatments, such as anti-TNF-α or anti-IL-6, which have shown adverse lipid modifications. Indeed, CIRT and CANTOS should help to provide the clinical community with additional evidence to determine whether reducing inflammation can reduce CV rates.

Author contributions

Both the authors have contributed to the design, analysis, development, critical revisions and final approval of the manuscript.

Conflicts of interest

Alberto J. Lorenzatti is a member of the CANTOS Study Steering Committee. Brenda M. Retzlaff has no disclosures.

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