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REVIEW ARTICLE

Inflammation in Cardiovascular Disease: Current Status and Future Perspectives

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Abstract

Atherosclerosis has been defined as an inflammatory disease. Three decades of research have pointed to a pivotal role of interleukin 6 for many aspects of cardiovascular disease, not the least of which is atherosclerosis. In this review, experimental and clinical studies are reported on a timeline, exploring mechanisms and possible explanations that form the basis of current knowledge. Some successful clinical trials were proof of concept studies, showing that not only inflammatory biomarkers are related to cardiovascular outcomes, but also that decreasing inflammation can reduce cardiovascular events. Great advances have been made in the management of residual cardiovascular risk due to cholesterol, thrombosis, and metabolic diseases, but the next frontier now seems to be targeting inflammation. In the upcoming years, the importance of inflammation will be evaluated in high-risk patients with chronic kidney disease, after acute coronary heart disease or heart failure with preserved ejection fraction. Inflammation seems to precede the development of cardiovascular risk factors. Moreover, counseling for a heathy lifestyle and, when necessary, the use of cardiometabolic therapies capable of decreasing inflammation, might be important.

Pivotal contributions to the inflammatory theory of atherosclerosis

In the late 90s, Ross defined atherosclerosis as an inflammatory disease.[1] Shortly before his study, Ridker described that among apparently healthy men participating in the Physicians' Health Study, those in the upper quartile of high-sensitivity C-reactive protein (hsCRP) at baseline had three times the risk of myocardial infarction and two times the risk of ischemic stroke during a follow-up of eight years.[2] Details of the atherogenesis process, as well as the complex interaction of inflammatory cells, cytokines, and lipids, were better understood from the fascinating publications made by Libby.[3-5] The next step was the description of the major characteristics of the vulnerable atherosclerotic plaque for thrombotic outcomes.[6,7] Meta-analysis of observational studies confirmed the association between hsCRP, coronary heart disease, ischemic stroke, and mortality.[8] However, a causal role of CRP in coronary heart disease was considered unlikely, based mainly on a large Mendelian randomization study.[9] Thus, hsCRP, even without a causal role in cardiovascular disease, has become a useful and affordable marker for risk stratification or follow-up in clinical practice.[10,11] In the CARE study, a significant decrease in hsCRP levels was reported among those individuals treated with pravastatin.[12] In the AFCAPS/TexCAPS trial, statin therapy reduced coronary outcomes even in subjects with lower levels of LDL-C, but it did present higher CRP levels at baseline.[13] The proof that patients with relatively normal cholesterol levels, but at increased cardiovascular risk due to elevated CRP levels, could benefit from statin therapy, was demonstrated in the JUPITER trial.[14] However, the real proof of concept that treating inflammation per se, without changes in lipids, glucose, or blood pressure, came with the CANTOS trial.[15] In addition to the reduction of CRP caused by the monoclonal antibody anti-interleukin 1-beta (IL-1b), this therapy also decreased interleukin-6 (IL-6), a cytokine with a causal role in cardiovascular disease.[16] Interestingly, based on genetic studies, any benefit of a decrease in IL-6 seems proportional to the absolute reduction in hsCRP levels.[17] Intravascular ultrasound (IVUS) performed in patients with ST-elevation myocardial infarction (STEMI) revealed that significant improvement in the atherosclerotic plaque composition was reported among those patients

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receiving high-intensity statin therapy, showing the largest decrease in hsCRP levels.[18,19] More recently, low-cost anti-inflammatory therapy with colchicine successfully reduced cardiovascular outcomes in patients with acute or chronic coronary artery disease.[20,21]

Inflammatory and cholesterol residual risk

Recently, a collaborative analysis of three randomized trials (n = 31,245 patients) was performed to evaluate the importance of inflammation and cholesterol as determinants of future cardiovascular outcomes.[22] The study examined increasing quartiles of baseline hsCRP and of increasing baseline LDL-C as a predictors of cardiovascular deaths and all-cause deaths. The authors found that hsCRP was a stronger predictor of future cardiovascular events than was LDL-C. These findings suggested the need for combined therapies, including effective lipid-lowering and inflammatory-inhibition drugs to reduce residual cardiovascular risk.

The high degree of decline in LDL-C, with major benefits for cardiovascular outcomes, has been well established from robust meta-analysis.[23,24] However, the same applies to the degree of reduction in inflammatory markers, hsCRP[25] and IL-6[26] based on a large prospective trial. In the CANTOS trial, those patients receiving canakinumab (monoclonal antibody anti-interleukin 1-beta) who achieved IL-6 levels below the median, showed a 32% reduction in major cardiovascular events, a 52% decrease in cardiovascular mortality, and 48% lower rates of all-cause mortality.[26]

Fascinating findings were recently reported on the importance of inflammation to predict outcomes in patients with chronic kidney disease.[27] Among 9,151 stable patients with previous myocardial infarction, the contribution of residual cholesterol and inflammatory risk were evaluated. Among patients with an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m^2, as well as increasing quartiles of both inflammatory markers (hsCRP and IL-6) and lipid markers (LDL-C and non-HDL-C), were positively related to the risk of recurrent cardiovascular events. Conversely, among those patients with eGFR < 60 mL/min/1.73m^2, only the inflammatory markers (hsCRP and IL-6) were associated with cardiovascular outcomes. Furthermore, both inflammatory markers were predictors of total mortality, whereas LDL-C and non-HDL-C were not. Similar results were observed in an analysis stratified by albumin to creatinine ratio.

In addition to renal glomerular hemodynamics, inflammation appears to be related to the stage of chronic kidney disease. In this scenario, the amount of monocyte-derived microparticles were progressively greater according to the stage of chronic kidney disease.[28]

In the STABILITY trial,[29] 14,611 patients with chronic coronary heart disease had baseline levels of IL-6 and were followed up for a median of 3.7 years. Patients were categorized into those with normal eGFR (≥ 90 mL/min/1.73m^2), mildly decreased eGFR (60-90 mL/min/1.73m^2), and moderately to severely decreased eGFR level (<60 mL/min/1.73 m^2). High levels of IL-6 (≥ 2 ng/L) were associated with cardiovascular outcomes in all stages of chronic kidney disease.

Role of inflammation after acute myocardial infarction

The relevance of lymphocyte subtypes and circulating cytokines was examined in the BATTLE-AMI trial.[30] Circulating levels of IL-1beta, IL-4, IL-6, IL-10, and IL-18 were collected during the first day of an ST-segment elevation myocardial infarction (STEMI) in patients undergoing a pharmacoinvasive strategy. In this study, the amount of infarcted mass and left ventricular ejection fraction (LVEF) were determined by cardiac magnetic resonance imaging (cMRI). After 30 days of STEMI, marked improvement in the balance of pro- and anti-inflammatory cytokines was observed, except for IL-6.[31] Titers of IL-6 at baseline were associated with infarcted mass (rho = 0.41, P < 0.001) and inversely related to LVEF (rho = -0.38, P<0.001)[32]. In addition, hsCRP collected on the first day of STEMI, as well as B2 classic lymphocytes at day 30, were related to the LVEF.[32] All of these findings reinforce the core role of IL-6 in cardiovascular disease.

Ongoing clinical trials and perspectives

It has been progressively established that the cell signaling pathway involving the NOD-, LRR-, and pyrin domain-containing protein (NLRP3) inflammasome to IL-1beta to IL-6 to hsCRP is clearly implicated in cardiovascular disease.[33] Thus, inhibition of this pathway is of great interest for cardioprotection, and therapies targeting IL-6 can be considered a research priority among therapies aiming to reduce residual risk.

The phase 2 trial RESCUE[34] with ziltivekimab (a fully human monoclonal antibody directed against the IL-6 ligand), showed a marked decrease in inflammatory biomarkers, no

change in lipids [(except for a favorable reduction in Lp(a)], in addition to very good tolerability. In addition, in RESCUE, ziltivekimab reduced thrombotic markers (e.g. fibrinogen). Thus, a large clinical trial was the next step.

The ongoing Ziltivekimab Cardiovascular Outcomes Study (ZEUS) was designed to address the benefit of this medication in a large and high-risk population of patients with established atherosclerotic cardiovascular disease, chronic kidney disease, and elevated inflammatory biomarkers. Thus, ZEUS will answer if the high residual risk of this population can be safely reduced by the monthly injection of ziltivekimab.

Two additional clinical trials are on our horizon based on the potential benefits of IL-6 inhibition.[35] The first study will examine the benefit of IL-6 inhibition in patients with heart failure and preserved ejection fraction (HERMES), while the second will test if IL-6 inhibition improves outcomes in patients with acute coronary syndromes (ARTEMIS).

What are the triggers for inflammation?

Advanced atherosclerotic lesions contain cholesterol crystals in the necrotic core, a highly disregarded fact in atherosclerosis. However, a well-conducted experiment using new microscopic techniques showed that cholesterol crystals can be viewed early on in diet-induced atherosclerosis.[36] The presence of cholesterol crystals coincides with the appearance of inflammatory cells. This novel aspect in atherogenesis revealed the potential link between cholesterol and inflammation due to the activation of NLRP3-inflammasome and the cascade of IL-1b to IL-6.[36] Soon afterward, new mechanisms were reported for inflammasome activation, such as neutrophil extracellular traps, atheroprone flow, and local tissue hypoxia.[37]

Recurrent cardiovascular events are common after an acute myocardial infarction.[38,39] Inflammation can contribute to these repeated events, and one fascinating study showed a marked increase in monocyte recruitment in chronic atherosclerosis.[40] Thus, a systemic inflammatory state for many weeks after acute myocardial infarction may well contribute to recurring cardiovascular events.

Conclusions

After three decades of clinical and experimental research involving inflammation and cardiovascular disease, the cell signaling pathway involving NLRP3 inflammasome, subsequently triggering the IL-6 expression, was progressively established as a main therapeutic target. Ongoing clinical trials will establish the safety and benefits of IL-6 inhibition. The availability of hsCRP in clinical practice constitutes a very useful inflammatory marker, which points out the IL-6 pathway. Formerly used for risk stratification for lipid-lowering therapy, hsCRP can now be used to estimate residual cardiovascular risk and identify those individuals most likely to benefit from an anti-inflammatory therapy, and was progressively established as a main therapeutic target (Graphic 1).

Finally, uncontrolled cardiovascular risk factors, such as hypertension, obesity, diabetes, smoking, and sedentary lifestyle, are all common conditions related to inflammation.[41] Thus, changes in lifestyle and the choice of therapies (statins, RAS blockers, some glucose lowering agents) can result in a marked decrease in inflammatory biomarkers. Therefore, the use of anti-inflammatory agents is not the only way to decrease inflammation. This approach seems particularly important for primordial prevention, avoiding the development of risk factors for cardiovascular diseases.

Disclosures

Dr. Fonseca has served as steering committee member of the JUPITER trial and CANTOS trial.

Author Contributions

Conception and design of the research and writing of the manuscript: Fonseca FAH, Izar COM.

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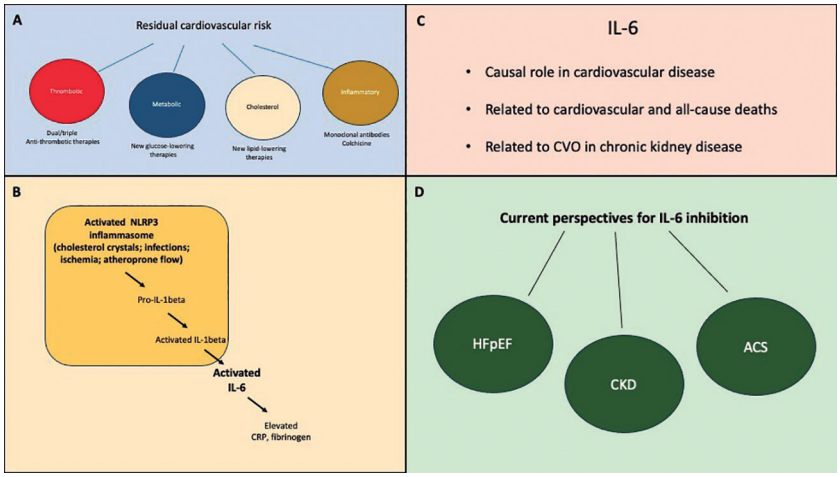
This article does not contain any studies with human participants or animals performed by any of the authors.



Graphic 1 – A. Residual cardiovascular risk has been lowered by therapies that have improved thrombotic, metabolic, and lipid risks. Promising therapies are now proposed to reduce residual inflammatory risk. B. Many stimuli can activate the NLRP3 inflammasome. Once activated by caspase 1, IL-1b is released into the blood stream and increases the expression of IL-6. Furthermore, expression of CRP, fibrinogen are also observed. C. Studies have suggested a pivotal role of IL-6 in outcomes related to cardiovascular and renal diseases. D. Decrease in inflammation targeting IL-6 has been proposed as the next frontier to reduce cardiovascular risk.
NLRP3 - NOD-, LRR-, and pyrin domain-containing protein; IL: interleukin; CRP: C-reactive protein; CVO: Cardiovascular Outcomes; CKD: Chronic Kidney Disease; ACS: Acute Coronary Syndrome; HFpEF: Heart Failure with Preserved Ejection Fraction.

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