The role of inflammation in atherosclerosis: what we have learned from clinical trials

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Abstract

Drugs that modify the classic risk factors of atherosclerosis remain the mainstay of care. However, although effective, there is still a need for adjunctive therapies to reduce further the risk of subsequent cardiovascular events. In the search for new targets to achieve this incremental benefit over standard therapies, inflammation features prominently and has been implicated in atherosclerotic disease progression and cardiovascular morbidity in descriptive studies. Consequently, suppressing inflammation has been the focus of multiple clinical trials. Most of these phase II and III trials have shown promising, but not definitive, results. In addition, some trials have suggested that inflammation has a protective role, with anti-inflammatory interventions actually increasing the risk of cardiac events. Consequently, anti-inflammatory therapies have not impacted on clinical practice. In this article we review descriptive studies, such as those of the accelerated atherosclerosis that affects transplanted hearts, which suggest an inflammatory etiology to atherosclerosis. We then summarize key interventional clinical trials that have directly examined the inflammatory hypothesis. ■ Heart Metab; 2013;60:9–13

Keywords: Atherosclerosis; coronary artery disease; inflammation.

Introduction

Over the past 30 years there have been considerable achievements in the primary and secondary prevention of cardiovascular events in patients with known atherosclerosis and/or merely with risk factors for disease [1]. Despite these advances atherosclerotic disease remains the most frequent cause of death in high and middle income countries. This is partly the result of the inadequate implementation of known effective therapies. However, even in those patients optimally treated the risk of future events remains high, acting as an impetus to find new therapeutic targets. Key observations, such as the accelerated atherosclerosis that is seen in the transplanted heart (allograft vasculopathy) prove the concept that inflammation can act as a "soloist" in the pathophysiology of the disease. Quenching inflammation may thus prevent a silent preclinical atheroma from becoming symptomatic and/or reduce the risk of future events in those with established clinical disease. What is the evidence that this is the case?

Established therapies are anti-inflammatory

Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) are very effective in reducing LDL cholesterol levels and cardiovascular events. Although these two factors are thought to have a cause–effect relationship, statins are also known to have an anti-inflammatory effect [2]. In numerous large scale trials,

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ABBREVIATIONS

hs CRP: high-sensitivity C-reactive protein; **IL-6**: interleukin-6; **LDL**: low-density lipoprotein; **MCP-1**: monocyte chemoattractant protein-1; **P38 MAPK**: P38 mitogen-activated protein kinase; **TNF**: tumor necrosis factor.

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they have proved effective in primary and secondary prevention of atherosclerotic events [3]. This clinical benefit is also achieved when they are used to suppress inflammation (as measured by lowering high sensitivity [hs] C-reactive protein [CRP]) in otherwise healthy individuals with normal lipid profiles, as shown in the JUPITER trial [4]. In this large randomized controlled trial, treatment with a statin resulted in a 50% reduction in vascular events in ostensibly healthy people with elevated hs-CRP in the absence of dyslipidemia at enrolment. Statins lowered the levels of both LDL and hs-CRP; however, the absolute risk reduction in vascular events was related to CRP and not LDL. Furthermore, lowering CRP in groups of patients without classic cardiovascular risk factors, other than advanced age, resulted in a clinical benefit similar to that observed in high-risk patients. Statins may thus have additional anti-inflammatory properties revealed by their effect in patients with active systemic inflammation, as revealed by hs-CRP, although this conclusion of the JUPITER trial remains a subject of intense debate.

The possibility that the anti-inflammatory effect of statins may contribute to their efficacy, as raised by JUPITER and observations from other statin trials, has driven a critical examination of whether more traditional anti-inflammatory agents may have similar benefits, especially when the residual vascular risk remains elevated after control of cholesterol and hypertension. We next review the pharmacological agents studied in clinical trials to suppress inflammation.

Traditional anti-inflammatory drugs

Different conventional anti-inflammatory drugs targeting varied inflammatory pathways have been tested in patients with symptomatic and silent atherosclerotic disease.

Paradoxically, non steroidal and steroidal anti-inflammatory drugs have proved harmful in patients with atherosclerosis. In fact, except for acetyl salicylic acid, non steroidal anti-inflammatory drugs, especially selective cyclooxygenase 2 inhibitors, increase morbidity and mortality in patients with coronary heart disease

[5, 6]. The cause of this increased risk is unknown but may relate to these agents promoting salt retention and thus elevating blood pressure or attenuating the antithrombotic function of the vascular endothelium. They may also antagonize the benefits of low-dose acetyl salicylic acid on platelet function. Initiated in 2006 and still actively recruiting, the PRECISION trial (NCT00346216) is comparing celecoxib, a selective cyclooxygenase 2 inhibitor, with two other non selective inhibitors in patients with, or at high risk of, cardiovascular disease.

Steroidal agents, the traditional potent immunomodulators, are a known cause of secondary dyslipoproteinemia and accelerated atherosclerosis. A current trial, however, is evaluating the effects of PEG-liposomal prednisolone sodium phosphate, on atherosclerotic plaque inflammation as measured by positron emission tomography–computed tomography imaging (NCT01601106).

Colchicine is another anti-inflammatory drug that inhibits the expression of adhesion molecules on T cells and endothelial cells, the synthesis of TNF and interleukin (IL)-6 and the secretion of metalloproteinase 9. It has been used successfully to block inflammation in gout and pericarditis, and is currently being investigated for other cardiovascular indications. In a clinical study, colchicine was found not to differ from placebo in suppressing inflammatory markers (hs-CRP) in patients with acute coronary syndrome or stroke [7], whereas low-dose colchicine (0.5 mg/day) was effective in the secondary prevention of cardiovascular events in patients with stable coronary disease in another study [8].

Early observational data from patients with rheumatoid and psoriatic arthritis suggest that anti-inflammatory agents used in these inflammatory disorders can result in a concomitant reduction in the risk of cardiovascular disease. Patients taking methotrexate, a drug with multiple molecular and cellular inflammatory targets, had an 18% lower risk of myocardial infarction and a 21% reduction in total cardiovascular disease in a meta-analysis of multiple rheumatoid/psoriatic arthritis studies [9].

On the basis of these previous results, a prospective randomized large scale study has just been initiated to examine if suppressing inflammation with low-dose methotrexate (15–20 mg/week) will lower the rate of major cardiovascular events (myocardial infarction, stroke and cardiovascular death) in patients

with known stable coronary artery disease/post myocardial infarction who also have one of the known common proinflammatory diseases: diabetes mellitus type 2 or metabolic syndrome. The study, the Cardiovascular Inflammation Reduction Trial (CIRT), is one of the major clinical studies interrogating the inflammatory hypothesis of atherosclerosis against the background of optimal medical therapy, therefore it should provide information on whether this is a viable additional target.

Antioxidants

Oxidation of lipoproteins in the arterial wall is one of the early processes in atheroma formation that is thought to act as a stimulus for the innate and adaptive immune responses driving inflammation. However, reactive oxygen and nitrogen species also play a role in causing endothelial dysfunction, which may contribute to atherosclerosis independent of inflammation. Therefore, blocking oxidative stress is theoretically attractive in primary and secondary prevention. Furthermore, statins and angiotensin converting enzyme inhibitors have known antioxidative effects that may contribute to their efficacy. Despite this apparent solid theoretical foundation, classic antioxidative agents such as vitamins E, A and C hold no clinical benefit over placebo in well-controlled and randomized trials, a conclusion reinforced in a large meta-analysis [10].

Another antioxidative agent, succinobucol, the monosuccinic acid ester of probucol, which inhibits TNF-inducible expression of different adhesion molecules (vascular cell adhesion molecule 1, monocyte chemoattractant protein-1 and E-selectin), has also failed in one study [11] to lower the primary composite outcome of cardiovascular death, resuscitated cardiac arrest, non fatal myocardial infarction, non fatal stroke, unstable angina, or coronary revascularization. However, succinobucol was associated with a small but significant reduction in the clinical burden of atherosclerosis that excluded unstable angina and coronary revascularization. The drug had a favorable effect on glucose control and noticeably lowered the incidence of new-onset diabetes mellitus.

Interleukin inhibitors

The role of interleukins as inflammatory modulators in chronic collagen vascular diseases is well established. While IL-1, IL-6 and TNF are known proatherosclerotic mediators, IL-10 and transforming growth factor have anti-inflammatory properties. In atherosclerosis, IL-1 seems to play a role in plaque initiation, instability and subsequent clinical events [12].

The successful clinical application of antagonists of proinflammatory interleukins (mainly IL-1) in rheumatoid arthritis has inspired their use in patients with atherothrombotic disease. Currently, three agents have progressed to phase II (anakinra and rilonacept) or phase III clinical studies (canakinomab) for atherosclerosis.

Canakinomab is a humanized monoclonal antibody to IL-1β, which is being evaluated in a large scale randomized controlled trial (the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study [CANTOS]; NCT01327846) in patients with previous myocardial infarction who have active persistent inflammation as measured by elevated hs-CRP. The study (CANTOS) is expected to be completed in 2016 and will demonstrate whether cardiovascular events (recurrent myocardial infarction, stroke and cardiovascular death) can be reduced by canakinomab. In common with the CIRT trial (see above) the placebo group includes optimal secondary prevention therapies. At the same time, the incidence of other disorders in which inflammation may play a pathogenic role such as diabetes mellitus, atrial fibrillation and thromboembolism will be co-interrogated.

Leukotriene inhibitors

Leukotrienes are arachidonic acid derivatives synthesized through the 5-lipoxygenase enzyme pathway. They potentially contribute to the atherosclerotic process through vasoactive effects and/or direct cellular action (on endothelial, vascular smooth muscle and circulating mononuclear blood cells). Aside from their role in the preclinical phase of the disease they have been found to associate with plaque instability and rupture [13].

Leukotrienes have been blocked by either targeting their synthesis (inhibition of the 5-lipoxygenase enzyme or one of the other key enzymes of the leukotriene synthetic pathway) or by blocking their receptors (cysteinyl leukotriene 1 receptor). VIA 2291, an inhibitor of 5-lipoxygenase, was shown to decrease inflammatory markers and unstable plaque burden, as evaluated by the volume of non calcified plaques on multislice coronary computed tomography angiography in patients with recent acute coronary syndrome [14]. Furthermore, montelukast, a leukotriene receptor antagonist, was found in a retrospective observational study to be associated with a lower incidence of my-

ocardial infarction in men and a lower incidence of stroke in both men and women who used this drug to control their asthma [15].

p38-MAPK inhibitors

This enzyme has pleiotropic biological functions including the initiation and progression of atherosclerosis in animal models. Losmapimod is a selective inhibitor of the alpha and beta isoforms of p38-mitogen-activated protein kinase (MAPK) that has been studied in patients with clinically stable atherosclerotic disease. Losmapimod was shown in this placebo-controlled study to lower inflammatory markers (hs-CRP) and to decrease inflammation, as measured by [^{18}F]2-fluoro-2-deoxyglucose positron emission tomography/computed tomography imaging, in the aorta and carotid arteries [16].

The positive effect of losmapimod on inflamed atherosclerotic plaques in the aorta and carotids encouraged a trial in non-ST-segment elevation myocardial infarction, SOLSTICE (NCT00910962) (the Study of Losmapimod Treatment on Inflammation and Infarct Size) [17]. This recently completed phase IIb placebo-controlled trial revealed promising signals on inflammation (CRP), other biomarkers such as brain natriuretic peptide and infarct imaging endpoints, leading to an upcoming phase III trial.

P-selectin antibodies

P-selectin is one of the adhesion molecules expressed on the surface of endothelial cells and platelets. It facilitates the recruitment of inflammatory cells (mononuclear and T lymphocytes) to the arterial wall in inflammation, atherothrombotic disease, and vascular healing [18–20].

Therapeutic antibodies blocking P-selectin have been studied in separate trials in two settings: SELECT–ACS and SELECT–CABG. In first study, SELECT–ACS, the P-selectin antibody, inclacumab, was compared to placebo in non-ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention. Inclacumab resulted in a smaller area of myocardial damage as measured by serum troponin and creatine kinase myocardial type at 16 and 24 hours post procedure [21]. The other ongoing study, SELECT–CABG, is examining whether inclacumab lowers venous conduit disease during the first year following coronary artery bypass graft surgery.

Conclusion

Accumulating evidence suggests blocking inflammation in atherosclerosis could complement standard cardiovascular prevention to reduce further the risk of future events. However, this evidence is not conclusive and is best viewed as work in progress. Consequently, the only drugs currently recommended are the traditional agents such as statins and angiotensin converting enzyme inhibitors that include an anti-inflammatory action among their many pleiotropic effects. The results of two important proof-of-concept trials discussed above (CIRT and CANTOS) are eagerly awaited. Furthermore, confirmation of the benefits of p38-MAPK inhibitors and P-selectin antagonists may be forthcoming over the next few years. Until the results of such phase III studies are revealed, the pathogenic role of inflammation in human atherosclerosis remains uncertain. ■

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