Anti-inflammatory therapy for cardiovascular disease

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Abstract: Chronic subclinical inflammation is a central process in the pathogenesis of cardiovascular disease (CVD) and it has been linked with both the initiation and progression of atherosclerosis. Several pro-inflammatory cytokines, such as the C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) have been described as independent risk factors for coronary heart disease and promoters of atherogenesis. Thus, extensive research is being conducted to assess the role of anti-inflammatory therapy in the primary and secondary prevention of CVD. Our review aims to provide the clinical and scientific data pertaining to the effects of different anti-inflammatory agents administered in patients with CVD.

Keywords: Inflammation; pro-inflammatory cytokines; anti-inflammatory agents/therapy; cardiovascular disease (CVD)

Introduction

Even though inflammation is an essential defense mechanism and body response, persistent elevation of certain pro-inflammatory biomarkers results in a chronic state of subclinical or low-grade inflammation, which has been identified as a key component in the development of cardiovascular disease (CVD) (1-3).

In this regard, C-reactive protein (CRP) is considered an active mediator in the pathogenesis of vascular disease and a predictor of endothelial dysfunction (4), which is now recognized as one of the earliest reversible precursors of atherosclerosis (5).

CRP increases smooth muscle cell migration and proliferation and vascular remodeling via angiotensin type 1 receptor upregulation and the generation of reactive oxygen species (ROS) (6). In addition, CRP facilitates the release of tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β) and interleukin-6 (IL-6) by macrophages and foam cells in the neointima (7). The release of these pro-inflammatory cytokines promotes atherogenesis by enhancing the release of adhesion molecules, resulting in early monocyte and lymphocyte recruitment in the intima (8). Furthermore, these pro-inflammatory cytokines are considered decisive factors in the pathogenesis and mortality of heart failure (9).

On the other hand, circulating monocytes, neutrophils and platelets have been also shown to be strong predictors of adverse cardiovascular (CV) events (10-13).

Based on the above, extensive research is being conducted to assess the role of anti-inflammatory therapy in the primary and secondary prevention of CVD. Our review aims to provide the clinical and scientific data pertaining to the effects of different anti-inflammatory agents administered in patients with CVD.

Anti-inflammatory agents in the management of CVD

Colchicine

Colchicine, which was initially used only for the treatment of gout, presents unique anti-inflammatory properties,

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as it promotes the disruption of microtubules, inhibits neutrophil chemotaxis, disrupts inflammasome functionality and inhibits cytokine production (14,15).

Due to its effects on cytokine production and neutrophil functionality, which have been linked to the progression of atherosclerotic disease (8,10,11), this drug has raised interest regarding its role in the prevention and management of CVD. By inhibiting neutrophil function, colchicine may lower the risk of plaque instability resulting in the reduction of disease progression.

The LoDoCo (low-dose colchicine) trial was a prospective, randomized trial, which evaluated 532 patients with stable coronary artery disease (CAD), of which 282 were treated with colchicine 0.5 mg/day. The majority of the patients were on aspirin/clopidogrel and statin therapy. Colchicine therapy significantly reduced the risk of the primary endpoint [incidence of acute coronary syndrome (ACS), out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke] by 67% (16).

In another cohort study, use of colchicine, administered in patients with gout, was associated with a 49% lower risk of adverse CV events, as well as a 73% reduction in all-cause mortality (14).

Furthermore, in a very recent study, which included 80 patients with history of a recent ACS, colchicine therapy favorably modified coronary plaque, independent of high-dose statin therapy and significant low-density lipoprotein (LDL-C) reduction (17).

Hydroxychloroquine (HCQ)

HCQ, a disease-modifying antirheumatic drug (DMARD), is an immunosuppressant agent used in the management of certain autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), as well for the prevention and treatment of certain types of malaria (18).

It exerts its immunomodulatory properties by suppressing inflammatory pathways through the prevention of toll-like receptor activation, which is needed for the expression of interferon-regulated genes and for the production of TNF-α, a major component of the cell-mediated inflammatory response (18,19).

High-dose HCQ therapy (400 mg daily), has been independently associated with a 56.8% reduced risk for CV morbidity in patients with RA (20).

In a retrospective study, which included 1,266 patients with incident RA (excluding patients with CVD prior to RA diagnosis), HCQ use was associated with a 72% reduction

in the risk of incident CVD and a 70% reduction in the risk of the composite incident CAD, stroke, and transient ischemic attack (TIA) (21).

Furthermore, there is evidence that HCQ exhibits hypolipidemic, hypoglycemic and antithrombotic properties when administered in patients with autoimmune diseases, such as RA or SLE (19,22-24), which may significantly contribute in the reduction of the risk for CVD conferred by HCQ in these patients.

Canakinumab

Canakinumab is a fully human monoclonal antibody, which inhibits inflammation by targeting IL-1β. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was a randomized, double-blind trial, which evaluated the CV effects of 3 different doses of canakinumab (50, 150, and 300 mg, administered subcutaneously every 3 months) *vs.* placebo in 10,061 patients with previous myocardial infarction (MI) and a high-sensitivity CRP (hsCRP) level ≥2 mg/L. The primary efficacy end point was the composite of nonfatal MI, nonfatal stroke, or CV death and the secondary end point was the composite of the primary endpoint plus hospitalization for unstable angina that led to urgent revascularization. After a median follow-up period of 3.7 years, treatment with the 150-mg dose of canakinumab (but not the other doses) led to a statistically significant 15% reduction in the primary end point and 17% reduction in the secondary end point, as compared with placebo. The median hsCRP level from baseline was reduced by 37% compared with placebo. All-cause mortality did not differ significantly between the canakinumab and placebo groups (25).

Methotrexate (MTX)

MTX is another DMARD used in the management of RA. This agent is a folic acid antagonist that inhibits the synthesis of purines and pyrimidines by inhibiting several key enzymes, including dihydrofolate reductase and thymidylate synthase. MTX decreases antigen-dependent T-cell proliferation and inhibits adenosine deaminase and adenosine monophosphate deaminase (AMP deaminase), resulting in the release of adenosine, a molecule with anti-inflammatory properties (26).

MTX appears to have anti-atherogenic properties, which may be due to the MTX-induced adenosine A2A receptor activation, leading to an enhancement of reverse cholesterol transport (RCT) and to a reduction of foam cell formation

in THP-1 macrophages (27). Furthermore, MTX reduces signal transducer and activator of transcription (STAT) protein activity, which is a known suppressor of RCT (28).

In addition, there is clinical evidence showing that MTX therapy in patients with RA is associated with less severe atherosclerotic disease and reduced risk for CVD (29,30). Actually, the cardioprotective effects of MTX therapy appear to be greater than those observed with other DMARDs (29,30). In a meta-analysis, which included 27 studies, it was shown that MTX use in patients with RA was associated with a 28% reduced risk for adverse CV events and a 19% reduced risk for MI when compared with other DMARDs (30). Furthermore, there is study evidence demonstrating that MTX therapy in patients with RA is associated with a 70% reduction in CV mortality (31) and a 60–70% reduction in total mortality (31,32).

However, more recent clinical evidence from the Cardiovascular Inflammation Reduction Trial (CIRT) has come to challenge the above presented clinical data regarding the cardioprotective effects of MTX. CIRT was a randomized, double-blind, placebo-controlled trial, which evaluated the anti-inflammatory and CV effects of low-dose MTX therapy (target dose of 15–20 mg weekly) *vs.* placebo in 4,786 patients with previous MI or multivessel CAD who, in addition, had either type 2 diabetes mellitus or the metabolic syndrome. After a median follow-up of 2.3 years, low-dose MTX did not reduce the levels of the pro-inflammatory biomarkers IL-1β, IL-6, or CRP when compared with placebo. More importantly, low-dose MTX, when compared with placebo, failed to reduce the adverse CV events comprising the original primary end point (composite of nonfatal MI, nonfatal stroke, or CV death) and did not also reduce the adverse CV events comprising the final primary end point (original primary endpoint plus hospitalization for unstable angina that led to urgent revascularization) (33).

These findings of CIRT differ from those in CANTOS and the authors suggested that the inconsistent cardioprotective effects of different anti-inflammatory agents may be a reflection of the distinct pathways targeted (33).

5-lipoxygenase (5-LO) inhibitors

5-LO is the key enzyme involved in the arachidonic acid (AA) cascade and catalyzes the synthesis of leukotrienes (LTs), including the two major active types, the non-cysteine-containing dihydroxyleukotriene B_4 (LTB4) and the cysteinyl leukotrienes LTC4, LTD4, and LTE4 (34).

LTB4 stimulates recruitment of monocytes, T lymphocytes and neutrophil granulocytes and promotes leukocyte adhesion to vascular endothelium, increases vascular permeability and enhances vascular smooth muscle cell proliferation and migration (35). Cysteinyl leukotrienes LTC4, LTD4, and LTE4 are major vasoconstrictors, contribute to thrombosis, enhance vascular permeability and stimulate proliferation of arterial smooth muscle cells (35).

Studies have shown an increased 5-LO expression in unstable atheroma and among those with chronic ischemia (36). Moreover, the number of 5-LO expressing cells is markedly increased in advanced atherosclerotic lesions of the aorta, coronary arteries or carotid arteries (37).

In view of their biomolecular properties, LTs are considered powerful inflammatory mediators that play a vital role not only in the pathogenesis of asthma, but also in the development of atherogenesis and CVD (34,38). This has raised an interest in creating a pharmacological approach to directly or indirectly block the 5-LO/LT pathway as a potential therapeutic target for CVD.

A drug being currently investigated is the VIA-2291 or Atreleuton, a selective 5-LO inhibitor, which has shown promising initial results. In a study, which assessed plaque progression via serial cardiac computed tomographic angiography (CCTA) in 54 patients with recent ACS, the use of Atreleuton resulted in a slowed plaque progression compared to placebo across different plaque subtypes (39).

In another double blinded, randomized study, which evaluated the efficacy of Atreleuton therapy versus placebo in patients with recent ACS, treatment with Atreleuton resulted in a decreased LT production and a reduced volume of noncalcified coronary plaque (40), the type of plaque more prone to rupture and to cause ACS (41). However, further large studies are needed to define the potential therapeutic role of 5-LO inhibitors in CVD.

Phospholipase A2 (PLA$_2$) inhibitors

PLA$_2$ is a widely distributed group of enzymes found in many isoforms, including the lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$), cytosolic phospholipase A$_2$ (cPLA$_2$) and secretory phospholipase A$_2$ (sPLA$_2$) (42).

PLA$_2$ enzymes hydrolyze phospholipids to generate free fatty acids and lysolipids, which are key components for the biosynthesis of eicosanoids and platelet-activating factor (PAF), thus potently promoting inflammation and atherogenesis (43,44). Both, Lp-PLA$_2$ and sPLA$_2$ are expressed primarily in pro-atherogenic inflammatory cells

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including macrophages, monocytes and lymphocytes (42,44). Furthermore, several sPLA$_2$ are expressed with various patterns in all stages of atherosclerosis development (44,45).

In addition, both Lp-PLA$_2$ and sPLA$_2$, to a different extent, are carried by LDL and generate lysophosphatidylcholine (Lyso-PC) and oxidized fatty acid (oxFA), two pro-inflammatory mediators promoting cell activation and production of inflammatory cytokines. Furthermore, Lyso-PC may also perpetuate vascular inflammation and promote necrotic core formation in atheromatous plaques, thus making plaques susceptible to rupture (46).

Given the above described pro-inflammatory and pro-atherogenic properties of PLA$_2$ enzymes, it becomes well understandable why PLA$_2$ inhibitors have received considerable attention in the medical research field as drug targets for the prevention and management of CVD. Two PLA$_2$ inhibitors have been developed, varespladib and darapladib.

Unfortunately, studies have not yet shown any positive outcomes with the use of PLA$_2$ inhibitors. VISTA-16 was a multinational, double-blind, randomized, multicenter clinical trial, which studied 5,145 patients within 96 hours of presentation of an ACS. The patients were randomized to receive either varespladib (500 mg daily) or placebo for 16 weeks, in addition to standard-of-care (SOC) therapy (including atorvastatin). Varespladib, when compared with placebo, failed to reduce the adverse CV events comprising the primary end point (composite of CV mortality, nonfatal MI, nonfatal stroke, or unstable angina with evidence of ischemia requiring hospitalization) and did not also reduce the adverse CV events comprising the secondary end point (composite of CV mortality, MI, and stroke). Varespladib was actually associated with a greater risk of MI, as compared with placebo (47).

SOLID-TIMI 52 was another multinational, double-blind, placebo-controlled trial that randomized 13,026 participants within 30 days of hospitalization with an ACS to receive either darapladib (160 mg daily) or placebo, in addition to SOC therapy. After a median follow-up period of 2.5 years, darapladib, as compared with placebo, did not reduce the incidence of the primary end point (composite of coronary heart disease death, MI, or urgent coronary revascularization for myocardial ischemia). In addition, darapladib failed to reduce the rates of any additional secondary end points, or any individual components of the primary end point, or all-cause mortality (48).

STABILITY was a double-blind clinical trial that randomized 15,828 patients with stable coronary heart disease to receive either darapladib (160 mg daily) or placebo, in addition to SOC therapy. After a median follow-up period of 3.7 years, darapladib, as compared with placebo, did not reduce the incidence of the primary end point (composite of CV death, MI, or stroke). In addition, darapladib failed to reduce the rates of the individual components of the primary end point or all-cause mortality (49).

Activin A

Activin A is a dimeric glycoprotein that belongs to the transforming growth factor-beta (TGF-β) super-family, originally described for its capacity to stimulate follicle-stimulating hormone (FSH). Aside from its effects on the reproductive system, activin A is recognized as a multifunctional cytokine, which is involved in a variety of biological processes, such as development, homeostasis, cell differentiation, tissue remodeling, inflammation and atherogenesis (50-52). It has been demonstrated that activin A can possess anti-inflammatory or pro-inflammatory effects depending on several factors, such as a different degree of cellular pre-activation, different expression pattern of the activin A receptors and others (52,53).

There is evidence that higher activin A levels predict worse left ventricular remodeling and all-cause mortality in patients with ST-elevation MI (54). Furthermore, there is also evidence that activin A is associated with the severity of coronary atherosclerotic burden and is independently associated with CV events and mortality in patients with type 2 diabetes mellitus (55,56). In addition, even in patients with pre-diabetes, a positive association has been demonstrated between circulating levels of activin A and carotid intima-media thickness, a well-established marker of atherosclerosis (57).

However, as mentioned earlier, activin A can also present anti-inflammatory properties, which may provide anti-atherogenic effects by inhibiting the release of pro-inflammatory cytokines, such as, IL-6, IL-8, and macrophage inflammatory protein (MIP)-1-alpha in patients with CAD (52). Studies have also suggested that activin A may be beneficially involved in atherogenesis by promoting plaque stabilization through the inhibition of foam cell formation and inducing differentiation of neointimal smooth muscle cells (52).

Hence, given the above, further studies are required to

more definitely determine the potential therapeutic use of activin A agonists and antagonists in the management CVD.

Conclusions

It has been well established that systemic inflammation plays an important role in both the initiation and progression of CVD. From the above review of the clinical and scientific data, one can conclude that anti-inflammatory therapy targeting specific pro-inflammatory mediators may, in certain instances, confer protection against CVD and thus it can provide a different therapeutic approach in the management of CVD. However, not all anti-inflammatory agents tested in clinical trials provided a beneficial CV effect and this raises the possibility that the specific anti-inflammatory pathway targeted may be crucial for the realization of true CV benefit.

Given the above, it becomes evident that further randomized controlled trials are required to more definitely determine the therapeutic potential of different anti-inflammatory agents in the management of CVD.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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