

Rheumatoid Arthritis and Atherosclerosis

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ABSTRACT: Inflammation is the basic mechanism leading to many pathological processes, including degenerative diseases, atherosclerosis, and cancer. We found an interesting link connecting rheumatoid arthritis and atherosclerosis that may explain the high cardiovascular event rate among patients with rheumatoid arthritis, but also may lead to a new way of thinking and a better understanding of atherosclerosis. Rheumatoid arthritis could serve as a model of accelerated atherosclerosis. Understanding the basic mechanisms of rheumatoid arthritis may solve some of the complexity of atherosclerosis.

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Patients with rheumatoid arthritis (RA) have an increased mortality rate due to cardiovascular events. Increased inflammation associated with RA is the main mechanism that leads to the increased rate of cardiovascular mortality. These data may suggest that aggressive management of inflammation may lower cardiovascular risk in patients with RA [1]. Women with RA had a twofold to threefold increased risk of myocardial infarction (MI), even without the traditional cardiovascular risk factors [2]. The increased cardiovascular morbidity in RA patients raises questions about the mechanisms that contribute to cardiovascular death in RA, how to identify high risk patients, and the effects of traditional prevention strategies and RA directed therapies on cardiovascular morbidity and mortality in patients with RA [3-5].

The extent of systemic inflammation could predict the poor cardiovascular outcome in patients with RA, but what are the mechanisms that link between systemic inflammation and cardiovascular risk?

Higher swollen joint counts and higher average C-reactive protein (CRP) levels were associated with carotid intima-medial plaques in patients with RA [4]. The European League against Rheumatism (EULAR) guidelines recommended aggressive management of the traditional risk factors in patients with RA. Several cardiovascular risk calculators are available, but most of these calculators do not consider RA as a risk factor. The EULAR

Endothelial function and endothelial progenitor cells are impaired in patients with rheumatoid arthritis

guidelines recommend to multiply by a factor of 1.5 to predict the cardiovascular risk in patients with RA [5]. RA patients have a twofold risk to develop silent MI, and they have more coronary plaques even without a clinical history of coronary artery disease [6]. Patients with RA show an increased 30-day post-MI mortality rate of 17.6% compared to 10.8% in non-RA subjects [7,8]. A meta-analysis of 111,758 patients with 22,927 cardiovascular events found a 50% increased risk of cardiovascular death in RA patients compared to the general population [8]. A 60% increased cardiovascular death (compared to non-RA subjects) was reported in another study [9]. The Nurses' Health Study reported that women with RA had a 45% increased cardiovascular mortality rate with a hazard ratio (HR) of 1.5 compared to non-RA women [10]. Cardiovascular mortality was associated with severity of inflammation, *HLA-DRB1*0404* gene type, and the presence of RA autoantibodies [8-10].

VULNERABLE CORONARY PLAQUES IN RHEUMATOID ARTHRITIS? Vulnerable, non-calcified coronary plaques were found in asymptomatic RA patients with a higher prevalence, extent, and severity (54% of RA patients) compared to controls (21% of controls, $P = 0.0001$) [11]. An autopsy study found that RA patients had significantly more vulnerable plaques than autopsy controls. A vulnerable plaque was defined by the number of inflammatory cells (> 25) per high power field with a thin fibrous cap ($< 65 \mu\text{m}$ thick) [12].

INFLAMMATION AND CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS

Inflammation is considered a key mechanistic pathway in atherosclerosis. Active inflammatory processes have been shown to trigger plaque rupture leading to acute vascular occlusion, acute myocardial infarction, and cerebrovascular stroke. IL-1 β is a pro-inflammatory cytokine that has a pivotal role in the inflammatory response, triggered by inflammatory pathways like interleukin 6 (IL-6) signaling pathway. Studies suggested that an imbalance between NET formation and NET degradation may be the mechanism behind autoimmune diseases. Neutrophils, interleukin 8, and anti-neutrophil cytoplasmic antibodies all play an active role in NET formation, which leads to prolonged exposure to NETs related events and increase the likelihood of systemic organ damage [13]. Premature accelerated atherosclerosis

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rotic coronary artery disease and premature cardiac death were related to interleukin 17A, a cytokine that acts on blood vessel cells and on myocardial cells, enhancing inflammation, coagulation, and thrombosis.

IL-1 β is a pro-inflammatory cytokine and member of the IL-1 family that regulates recruitment and activation of cells involved in the immune response [13].

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study [CANTOS], a randomized clinical trial that examined the inflammatory hypothesis in atherosclerosis [14], recruited patients with a history of MI and documented chronic inflammation (high CRP levels). They were randomized to Canakinumab at doses of 50, 150, and 300 mg every 3 months or placebo. Canakinumab is an IL-1 blocker approved by the U.S. Food and Drug Administration for treatment of patients with juvenile idiopathic arthritis. The mean follow-up period was 3.7 years, with a significant decrease in risk of primary end points (nonfatal MI, stroke, or cardiovascular death) in patients treated with Canakinumab in all doses [14].

THE EFFECT OF HMG-COA REDUCTASE INHIBITORS (STATINS) ON RHEUMATOID ARTHRITIS

The beneficial effects of statins are beyond their effect on the lipid profile per se. Some of the mechanistic pathways that may explain the pleiotropic effects of statins include an effect on vascular inflammation. It has been demonstrated in endothelial cells and in monocyte-macrophages. Statins reduce TH1 responses (CD4+ helper T cells) and promote TH2 cell responses. These cells secrete anti-inflammatory cytokines like IL-4, IL-10, IL-13, and reduce level of transforming growth factor. Statins also increase levels of circulating endothelial progenitor cells (EPCs) in the blood flow due to improved mobilization from the bone marrow. This circulation augments neovascularization of ischemic tissue. Statins upregulate eNOS expression and prevent the inhibitory effect of oxidized LDL on eNOS. Statins prevented L-arginine methyl ester-induced decrease of klotho gene expression in rat kidneys, and prevented progression of atherosclerosis. Statins attenuate angiotensin II induced free radical production and downregulate angiotensin AT1-receptor expression. Statins induce impaired expression of tissue factor (TF) on macrophages, attributed to inhibition of the TF gene induction, that way they prevent hyper-coagulable state and thrombogenesis. Statins also inhibit Rho/Rho-kinase and activation of Akt, and attenuate atherosclerotic plaque thrombogenicity by inhibiting cell-mediated thrombin generation. Clinical data (a meta-analysis of 15 clinical studies) showed that statin therapy in patients with RA increased high density lipoprotein (HDL) cholesterol, reduced LDL-cholesterol, total cholesterol, and triglyceride levels. Statins decreased CRP and erythrocyte sedi-

Nitric oxide plays a key role in inflammation and atherosclerosis

mentation rate, and improved disease activity score (in patients who were treated with statins for 12 weeks) with reduction in the 28-joint disease activity score (DAS28) [15,16].

ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS

Endothelial dysfunction has been linked to systemic inflammation and accelerated atherosclerosis. Vascular responsiveness of patients with RA was impaired in most of the patients with RA (86%). Patients with the worst vascular parameters (severe endothelial dysfunction) had the worst clinical characteristics of RA [17]. An impaired function and lower numbers of EPCs in patients with RA were found, which could explain the endothelial dysfunction observed in most of the patients with RA [18]. The positive correlation between EPCs and endothelial function, as well as the cardiovascular risk assessed by the Framingham score, has been demonstrated. Subjects with cardiovascular risk factors had impaired number and function of their EPCs. The EPCs number was inversely correlated with endothelial function [19].

ENDOTHELIAL PROGENITOR CELLS IN RHEUMATOID ARTHRITIS

Reduction in EPCs number and function were documented in patients with coronary artery disease and stroke. In RA, levels of peripheral EPCs were inhibited compared with healthy controls, and an inverse correlation has been reported between peripheral EPCs level and disease activity. EPCs were also observed accumulating in inflamed joints, where an increased blood vessel supply is needed, giving rise to the hypothesis that EPCs are trapped within the highly vascularized joints. The trapped EPCs may contribute to disease progression by maintaining the inflammatory process through new blood vessels formation, further facilitating the influx of immune cells [20,21].

THE EFFECTS OF INFLAMMATION ON ENDOTHELIAL PROGENITOR CELLS

CRP inhibited EPCs differentiation, survival, and function. Even in healthy subjects, the colony-forming capacity was negatively correlated with level of CRP. CRP itself may impair EPCs anti-oxidant defense systems and may promote EPC sensitivity to oxidant-mediated apoptosis and telomerase inactivation. However, during an acute inflammation following an acute ischemic event CRP has a positive-regenerative role. Its release leads to rapid EPCs mobilization and mobilization to the organ in need. Together, these findings suggest a dual role of CRP in EPCs biology depending on the cause and duration of CRP secretion. The production of CRP in the liver is induced by pro-inflammatory cytokines like IL-6, IL-1, and IL-17 [22,23]. IL-6 plays a key role in inflammation of chronic inflammatory disorders, and high IL-6 levels were associated with low EPCs number in RA

Biological treatments are beneficial in reducing cardiovascular risk in rheumatoid arthritis patients

patients and in healthy controls, suggesting a potential role for IL-6 in EPCs homeostasis and biology. An acute increase in IL-6 activates EPCs mobilization, whereas chronic IL-6 secretion is associated with inhibition of peripheral EPCs [24,25].

Tumor necrosis factor alpha (TNF- α) is another pro-inflammatory cytokine highly upregulated in RA. In RA, increased TNF- α levels were associated with reduced numbers of EPCs, and patients treated with antibodies blocking TNF- α showed either normal EPC levels or an increased EPCs level. The addition of TNF- α to EPCs isolated from healthy controls led to a dose-dependent reduction of proliferation, migration, adhesion, and tube formation capacity. TNF increased EPCs apoptosis and enhanced expression of pro-inflammatory adhesion molecules and paracrine factors in EPCs. Several medications, like HMG-CoA reductase inhibitors (statins) or resveratrol found in red wine, can revert the inhibitory effect of TNF on EPCs and restore the number and function of EPCs in the peripheral circulation [26].

THE ROLE OF NITRIC OXIDE

Nitric oxide is a short-lived signaling molecule produced by vascular endothelial cells, which has a role in the homeostasis of the vascular tone. Nitric oxide also regulates cell survival, proliferation, and migration. Stimulation of nitric oxide production, or its signaling cascades in EPCs, increases EPCs number and function, thus attenuating endothelial damage. The enzyme that is responsible for nitric oxide production is the endothelial nitric oxide synthase (e-NOS). Mice deficient in e-NOS (Nos3 $^{-/-}$) showed reduced vascular endothelial growth factor (VEGF)-induced mobilization of EPCs with increased mortality. Intravenous infusion of wild-type progenitor cells rescued the defective neovascularization of Nos3 $^{-/-}$ mice in a model of hind-limb ischemia, suggesting that progenitor cell mobilization from the bone marrow was impaired in Nos3 $^{-/-}$ mice. Matrix metalloproteinase-9 (MMP-9), which is required for stem cells mobilization, was reduced in the bone marrow of Nos3 $^{-/-}$ mice. These findings indicate that e-NOS expression by bone marrow stromal cells has a role in the recruitment of stem cells and progenitor cells from the bone marrow to circulation [27,28].

THE EFFECT OF BIOLOGIC THERAPIES ON ATHEROSCLEROSIS

Anti-TNF medications

Drugs inhibiting TNF- α (TNF-inhibitors) have been shown to reduce joint inflammation and inflammatory markers; thus, they may also influence the future risk of MI in the general population. Studies found a reduced risk of MI following TNF-inhibitor treatment, compared with treatment with synthetic disease-modifying anti-rheumatic drugs (s-DMARDs). The British Society for Rheumatology Biologics Register for

Rheumatoid Arthritis was a UK-wide prospective observational study that was established in 2001 to monitor the long-term safety of TNF-inhibitors and other biological therapies. UK guidelines restricted the prescription of TNF-inhibitors in RA to patients with sustained active disease (DAS28 > 5.1) on at least two occasions one month apart who had failed to respond to therapeutic doses of ≥ 2 s-DMARDs (including methotrexate) given for 6 months or more. The TNF-inhibitor-treated patients included in this analysis received etanercept, infliximab, and adalimumab. The control group was a group of biologic-naïve patients with active disease (DAS28 > 4.2) who were treated with s-DMARD therapies only. A 39% reduction in risk of MI was found in patients treated with TNF inhibitors compared to the control group [29,30].

IL-1 inhibition

The inflammatory effects of IL-1 can be blocked by its inhibitor, IL-1 receptor antagonist (IL-1Ra), or by anakinra, a recombinant form of human IL-1Ra. Treatment with anakinra significantly improved vascular function and left ventricular function in patients with RA. This effect was much more pronounced in RA patients who had a documented coronary artery disease.

In the Diastolic Heart failure Anakinra Response Trial pilot study (12 patients), anakinra improved peak aerobic capacity in RA patients with heart failure. Other IL-1 inhibitors, like riloncept and canakinumab, have yet to be studied [31].

Biological treatments could be used to reduce atherosclerosis in patients presenting with atherosclerotic artery disease

IL-6 inhibition

Tocilizumab is a humanized monoclonal antibody that blocks IL-6 receptor and its IL-6-mediated pro-inflammatory signalling pathway. Six months of treatment with tocilizumab improved endothelial dysfunction and aortic stiffness. In a long-term study, the rates of MI and stroke decreased (0.25/100 patient-years and 0.19/100 patient-years) in patients who received tocilizumab compared with 0.49/100-person-years and 0.24/100-person-years in the control groups [32].

Rituximab

Studies examining the cardiovascular effects of rituximab, a chimeric anti-CD20 monoclonal antibody, in RA patients are limited. Significant improvements in endothelial dysfunction assessed through increased flow mediated diameter percent change have been noted with rituximab [33,34].

CONCLUSIONS

Chronic inflammation is the basic mechanism that causes impaired number and function of EPCs, endothelial dysfunction, plaque rupture, and post infarct remodeling; thus, inhibition of TNF- α may affect the inflammatory burden and plaque vulnerability leading to less cardiovascular events and

cardiovascular death. Aggressive management of inflammation may lead to a significant reduction of cardiovascular risk in patients with RA.

Inhibition of inflammation using biological medications that were primarily aimed to treat the high scale inflammation of RA may be useful to prevent progression of atherosclerosis in the general population.

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“The ideals which have lighted my way, and time after time have given me new courage to face life cheerfully, have been kindness, beauty, and truth”

Albert Einstein (1879–1955), German-born theoretical physicist who developed the theory of relativity, one of the two pillars of modern physics (alongside quantum mechanics)