Inflammation and endothelial dysfunction in rheumatoid arthritis

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At present, there is strong evidence to support an increased incidence of cardiovascular (CV) events and CV mortality in patients with rheumatoid arthritis (RA) (1, 2). This is a consequence of atherosclerosis (3, 4). Although in some cases the classic atherosclerosis risk factors known to promote the progression of atherosclerotic lesions may be absent (5), accelerated atherosclerosis has been observed in these patients (6).

Atherosclerosis is now considered an inflammatory disease. Affinities between the inflammatory mechanisms leading to atherosclerosis and those leading to the development of atherosclerotic disease in patients with RA have recently been emphasized (7). Subclinical atherosclerosis, manifested by increased carotid artery intima-media thickness and increased number of carotid plaques, was observed in patients with RA without classic CV risk factor or CV events (8). A significant linear trend for increased carotid intima-media thickness associated with increasing C-reactive protein (CRP) levels was found (9). In concordance with these observations, Goodson et al. showed that the baseline level of CRP is also a predictor of all-cause mortality, and specifically of CV mortality, in patients with inflammatory polyarthritis in a 10-year period following the onset of the rheumatic disease (10).

In the process of accelerated atherosclerosis in RA a major issue is the development of endothelial activation, which leads to endothelial dysfunction a premature atherosclerosis in these patients. Sattar et al. proposed that increased levels of circulating inflammatory mediators might cause activation and damage of endothelial cells (EC) in patients with RA (7). Since proinflammatory cytokines induce upregulation of MHC-class II molecules on EC, the presence of chronic inflammation in genetically predisposed individuals may explain at least in part the increased risk of CV events in patients with RA (11). With respect to this, a recent epidemiological study has emphasized the role of a chronically high inflammatory response in certain individuals carrying HLA-class II shared epitope alleles, in particular HLA-DRB1*0404, in the increased risk of CV events and CV mortality observed in RA (12).

A healthy endothelium prevents adhesion of mononuclear cells. Inflammation promotes EC activation, which is characterized by loss of vascular integrity, increased expression of leukocyte adhesion molecules, such as selectins, VCAM-1 and ICAM-1, change in phenotype from antithrombotic to thrombotic, production of several cytokines, and upregulation of MHC-HLA-class II molecules. All these changes allow EC to participate in the inflammatory response. In this process, the increased expression of adhesion molecules promotes the adherence and migration of monocytes into the vessel wall. Differentiation of monocytes into macrophages in the intima, activation and further differentiation to foam characterize the development of early atherosclerotic lesion (13, 14).

Nitric oxide (NO) is formed in EC from the amino acid L-arginin in the presence of the co-factor tetrahydrobipterin by the endothelial isoform of nitric oxide synthase (eNOS). Endothelial derived NO participates in several functions such as relaxing vascular smooth muscle cells, inhibition of platelet and leukocyte adhesion to vascular endothelium, inhibition of the vascular smooth muscle cell migration and growth, and limiting the oxidation of atherogenic low density lipoproteins. These actions suggest an atheroprotective role for endothelial NO in addition to its effect on vessel tone and blood pressure (15, 16). Reduced bioavailability of NO is considered the key feature of endothelial dysfunction. Continuous EC activation, manifested by increased levels of adhesion molecules sICAM-1 and sE-selectin is present in patients with RA (17), subsequently leads to endothelial dysfunction, which is an important event in early atherogenesis and also contributes to the development of clinical features in the later stages of the vascular disease including progression of the atherosclerotic plaque (18). Endothelial dysfunction is a recognized pathway variable in predicting develop-
ment of subsequent CV complications. This may be determined as an impaired ability of the artery to dilate in response to physical and chemical stimuli due to a decreased released or increased breakdown of NO (19). Interestingly, in patients undergoing vascular surgery an impaired flow-mediated dilatation of the brachial artery due to endothelial dysfunction independently predicted short-term CV events (20).

Bergholm et al. reported endothelial dysfunction in 10 newly treated patients with RA that received intrabrachial artery infusions of acetycholine (21). Likewise, using intrabrachial infusions of acetycholine in 8 patients with RA and 8 matched controls, Hansel et al. also reported the presence of endothelial dysfunction in long-term RA patients receiving standard methotrexate (MTX) therapy (22).

Endothelial function can more easily be non-invasively determined by post-occlusion flow-mediated vasodilatation of the brachial artery using high-sensitivity brachial ultrasonography (23, 24). Using this technique, we observed the presence of endothelial dysfunction in a series of 55 long-term treated patients with RA without clinically evident CV complications, expressed as decreased percentage of flow mediated endothelium-dependent vasodilatation (EDV) compared with matched controls (25). Italian investigators confirmed the presence of endothelial dysfunction, also expressed as a reduced percentage of flow-mediated EDV, in a series of 32 young to middle aged RA patients without traditional CV risk factors and low disease activity (26).

TNF-α plays an important role in the initiation and progression of inflammation in RA as well as in the mechanisms implicated the accelerated atherosclerosis in these patients (27). TNF-α blocks eNOS activation by interfering with the phosphorylation of protein kinase Akt (28). This proinflammatory cytokine also degrades eNOS mRNA (29). This impaired NO bioavailability is a primary manifestation of endothelial dysfunction, leading to impairment in EDV (30).

Chimeric anti-TNF-α monoclonal antibody- infliximab, alone or in combination with low-dose MTX, is an effective therapy in severe RA (31). Infliximab blocks inflammation by inhibiting the downstream effects of this cytokine (31). TNF-α blockade using the antagonist drug infliximab reduced disease activity and significantly improved endothelial function in 11 patients with active RA after 12 weeks of therapy (32). A significant improvement in EDV, which paralleled with the clinical improvement of the joint manifestations and with a decrease in the CRP and erythrocyte sedimentation values, was observed in this series (32).

Likewise, a recent study has disclosed that short-term adalimumab (a fully human monoclonal antibody directed against TNF-α) therapy also improves endothelial function in long-standing RA patients with severe disease refractory to infliximab (33).

In an attempt to determine the duration of effect of anti-TNF-α blockade on the endothelial function and whether the improvement of endothelial function after TNF-α blockade was still effective in long-term infliximab-treated RA patients, we performed serial measurements of endothelial function in a series of 7 RA patients who have been treated with infliximab for at least 1 year. Following infusion of the drug a dramatic and rapid increase in the percentage of EDV was observed. In all patients values of percentage of EDV at day 2 after infusion (mean: 9.4 %) were greater than those observed 2 days before infusion (mean: 2.8 %). At day 7 post-infusion, the percentage of EDV in all these patients was still significantly greater than before infusion. However, values returned to baseline by 4 weeks after infusion of the drug (34).

In keeping with these observations, another recent study from our group supported the evidence of progression of subclinical atherosclerosis in RA patients with severe disease despite periodical treatment with anti-TNF-α monoclonal antibody-infliximab (35). These observations suggest that the potential effect of anti-TNF-α therapy is transient and progression of atherosclerosis in patients with RA is in line with changes in systemic inflammatory levels. Indeed, as elegantly emphasized by Sattar and McInnes (36), systemic levels of proinflammatory cytokines generally remain dysregulated in patients with RA compared to individuals without this chronic disease and may promote the development of vascular disease and atherosclerosis.

Interestingly, Dessein et al. reported that endothelial dysfunction in RA was independently associated with circulating interleukin (IL)-6 concentration (37). In the present issue of *Clin Exp Rheumatol* the same group of investigators report a new study aimed to determine circulating cytokines (TNF-α, IL-1 and IL-6) as well as soluble adhesion molecules (ICAM-1, VCAM-1 and E-selectin) known to be biomarkers of endothelial dysfunction, before and after 2 weeks of high-dose intra-articular methylprednisolone therapy (38). Following this procedure, significant reductions in IL-6, which were associated with a decrease of the biomarkers of endothelial dysfunction was observed. However, no significant change in serum IL-1 and TNF-α levels were found. These results emphasize the role of IL-6 in the atherogenic process leading to RA and highlight the potential role of drugs specifically aimed at blocking IL-6 to reduce the progression of the atherosclerotic disease observed in patients with RA.

References

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