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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 tetrahydrobiopterin 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 acetylcholine (21). Likewise, using intrabrachial infusions of acetylcholine 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

1. GOODSON N, MARKS J, LUNT M, SYMMONS D: Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. *Ann Rheum Dis* 2005; 64: 1595-601.
2. SOLOMON DH, KARLSON EW, RIMM EB *et al.*: Cardiovascular Morbidity and Mortality in Women diagnosed with rheumatoid arthritis. *Circulation* 2003; 107: 1303-7.
3. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, MARTIN J: Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; 35: 8-17.
4. SHOENFELD Y, GERLI R, DORIA A *et al.*: Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation* 2005; 112: 3337-47.
5. DEL RINCÓN I, WILLIAMS K, STERN MP, FREEMAN GL, ESCALANTE A: High incidence of cardiovascular events in rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; 44: 2737-45.
6. DEL RINCON I, WILLIAMS K, STERN MP,

FREEMAN GL, O'LEARY DH, ESCALANTE A: Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. *Arthritis Rheum* 2003; 48: 1833-40.
7. SATTAR N, McCAREY DW, CAPELL H, McINNES IB: Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003; 108: 2957-63.
8. GONZALEZ-JUANATEY C, LLORCA J, TESTA A, REVUELTA, J GARCIA-PORRUA C, GONZALEZ-GAY MA: Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. *Medicine* (*Baltimore*) 2003; 82: 407-13.
9. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, PINEIRO A, GARCIA-PORRUA C, TESTA A, LLORCA J: High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32: 1219-23.
10. GOODSON NJ, SYMMONS DP, SCOTT DG, BUNN D, LUNT M, SILMAN AJ: Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year follow-up study of a primary care-based inception cohort. *Arthritis Rheum* 2005; 52: 2293-9.
11. TURESSON C: Endothelial expression of MHC class II molecules in autoimmune disease. *Curr Pharm Des* 2004; 10: 129-43.
12. GONZALEZ-GAY MA; GONZALEZ-JUANATEY C, LOPEZ-DIAZ *et al*.: HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2006 *(in press)*.
13. LIBBY P, RIDKER PM, MASERI A: Inflammation and atherosclerosis. *Circulation* 2002; 105: 1135-43.
14. BIJL M: Endothelial activation, endothelial dysfunction and premature atherosclerosis in systemic autoimmune diseases. *Neth J Med* 2003; 61: 273-7.
15. MONCADA S: Nitric oxide in the vasculature: physiology and pathophysiology. *Ann N Y Acad Sci* 1997; 811: 60-7.
16. IGNARRO LJ: Nitric oxide: a unique endogenous signaling molecule in vascular biology. *Biosci Rep* 1999; 19: 51-71.
17. WALLBERG-JONSSON S, CVETKOVIC JT, SUNDQVIST KG, LEFVERT AK, RANTAPAA-DAHLQVIST S: Activation of the immune system and inflammatory activity in relation to markers of atherothrombotic disease and atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2002; 29: 875-82.
18. VITA JA, KEANEY JF JR: Endothelial function: a barometer for cardiovascular risk? *Circulation* 2002; 106: 640-2.
19. NADAR S, BLANN AD, LIP GY: Endothelial dysfunction: methods of assessment and application to hypertension. *Curr Pharm Des* 2004; 10: 3591-605.
20. GOKCE N, KEANEY JF JR, HUNTER LM *et al*.: Risk stratification for postoperative cardiovascular events via non-invasive assessment of endothelial function: a prospective study. *Circulation.* 2002; 105: 1567-72.
21. BERGHOLM R, LEIRISALO-REPO M, VEHKAVAARA S, MAKIMATTILA S, TASKINEN MR, YKI-JARVINEN H: Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis. *Arterioscler Thromb Vasc Biol* 2002; 22: 1637-41.
22. HANSEL S, LASSIG G, PISTROSCH F, PASSAUER J: Endothelial dysfunction in young patients with long-term rheumatoid arthritis and low disease activity. *Atherosclerosis* 2003; 170: 177-80.
23. CELERMAJER DS, SORENSEN KE, GOOCH VM *et al*.: Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992; 340: 1111-5.
24. CORRETTI MC, ANDERSON TJ, BENJAMIN EJ *et al*.: Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002; 39: 257-65.
25. GONZALEZ-JUANATEY C, TESTA A, GARCIA-CASTELO A *et al*.: HLA-DRB1 status affects endothelial function in treated patients with rheumatoid arthritis. *Am J Med* 2003; 114: 647-52.
26. VAUDO G, MARCHESI S, GERLI R *et al*.: Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. *Ann Rheum Dis* 2004; 63: 31-5.
27. BACON PA, RAZA K, BANKS MJ, TOWNEND J, KITAS GD: The role of endothelial cell dysfunction in the cardiovascular mortality of RA. *Int Rev Immunol* 2002; 21: 1-17.
28. HERMANN C, ASSMUS B, URBICH C, ZEIHER AM, DIMMELER S: Insulin-mediated stimulation of protein kinase Akt: a potent survival signaling cascade for endothelial cells. *Arterioscler Thromb Vasc Biol* 2000; 20: 402-9.
29. YOSHIZUMI M, PERRELLA MA, BURNETT JC JR, LEE ME: Tumor necrosis factor downregulates an endothelial nitric oxide synthase mRNA by shortening its half-life. *Circ Res* 1993; 73: 205-9.
30. NAKAMURA M, YOSHIDA H, ARAKAWA N, SAITOH S, SATOH M, HIRAMORI K: Effects of tumor necrosis factor-alpha on basal and stimulated endothelium-dependent vasomotion in human resistance vessel. *J Cardiovasc Pharmacol* 2000; 36: 487-92.
31. IMPERATO AK, BINGHAM CO 3RD, ABRAMSON SB: Overview of benefit/risk of biological agents. *Clin Exp Rheumatol* 2004; 22: S108-14.
32. HÜRLIMANN D, FORSTER A, NOLL G *et al*.: Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation* 2002; 106: 2184-7.
33. GONZALEZ-JUANATEY C, LLORCA J, SANCHEZ-ANDRADE A, GARCIA-PORRUA C, MARTIN J, GONZALEZ-GAY MA: Short-term adalimumab therapy improves endothelial function in patients with rheumatoid arthritis refractory to infliximab. *Clin Exp Rheumatol* 2006 *(in press)*.
34. GONZALEZ-JUANATEY C, TESTA A, GARCIA-CASTELO A, GARCIA-PORRUA C, LLORCA J, GONZALEZ-GAY MA: Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. *Arthritis Rheum* 2004; 51: 447-50.
35. GONZALEZ-JUANATEY C, LLORCA J, GARCIA-PORRUA C, MARTIN J, GONZALEZ-GAY MA: Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. *Arthritis Rheum* 2006; 55: 150-3.
36. SATTAR N, MCINNES IB: Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. *Curr Opin Rheumatol* 2005; 17: 286-92.
37. DESSEIN PH, JOFFE BI, SINGH S: Biomarkers of endothelial dysfunction, cardiovascular risk factors and atherosclerosis in rheumatoid arthritis. *Arthritis Res Ther* 2005;7: R634-43.
38. DESSEIN PH, JOFFE BI: Suppression of circulating interleukin-6 concentration is associated with decreased endothelial activation in rheumatoid arthritis.*Clin Exp Rheumatol* 2006; 24: 161-167.