Atherosclerosis in Rheumatoid Arthritis

Paul Bacon
Dept of Rheumatology, University of Birmingham, UK

INTRODUCTION

The old adage that "rheumatoid patients have many problems – but they do not die of their disease" is now seen to be untrue. Mortality rates are in fact increased in RA in all countries examined, a consistent finding across >25 series.[1] Significant increases have been found in standardised mortality rates, of between 2 and 5. The major cause for this is coronary heart disease (CAD), which accounts for more than half the excess mortality.[2] The concept that the enhanced mortality relates to CAD is confirmed by several studies showing excess sub-clinical atherosclerosis in ultra-sound studies of the carotid arteries.[3] There is an inclination to think that this represents the end stage of persistent long-standing immune inflammation. In fact CAD is not a late complication of RA, since significant excess mortality is apparent within 5 years of disease onset.[4] Moreover, objective evidence of heart disease provided by SPECT scans have shown that myocardial perfusion abnormalities occur a decade earlier in RA than local controls.[5] Although women, who predominate in RA, have lower CAD rates than men, the excess CAD in RA is found in women as well as men.[4, 6] Thus it is now clear that RA patients have excess cardiovascular disease and mortality.

SYSTEMIC V SYNOVIAL DISEASE

The excess mortality is not accounted for simply by an excess of classic risk factors found in RA, although factors such as inactivity and obesity doubtless play a part. This suggests that RA itself may be a risk factor, similar to the well defined risk provided by diabetes. The challenge is to define which aspect of RA provides that risk. Atherosclerosis is now seen as an inflammatory immune disorder and inflammatory markers such as CRP appear as potent risk factors for development of atherosclerosis in epidemiological studies.[7] Thus the simplest hypothesis for RA would be that the synovial inflammation increases the overall inflammatory burden and hence the risk of CAD. However, the association is not with synovitis alone. Indeed in early disease, the risk in sero-negative cases otherwise classifiable as RA was equivalent to the general population. The data from several studies indicates that CAD is associated with sero-positive RA.[4, 6] A preliminary report has recently suggested that rheumatoid factor is also a risk factor in the general population, even in the absence of RA. The rheumatoid factor data, if confirmed, could indicate that the risk is a genetic one, predating the onset of arthritis. Other evidence supports the conclusion that the risk factor in RA relates to systemic rather than synovial disease. A strong link has also been shown between severe systemic RA with extra-articular features and CAD.[8] Indeed CAD itself may be an extra-articular feature of RA.[9]

VASCULAR INFLAMMATION AND ATHEROGENESIS

We have pursued the hypothesis that vascular inflammation is the major extra-articular feature in the accelerated atherogenesis seen in RA.[10] Clinical vasculitis is rare in RA but sub-clinical vascular inflammation occurs in around one-third.[11] Such vascular inflammation is a major feature of the "severe ex-RA" defined by.[12] Well established studies have linked local vascular inflammation to subsequent development of atherosclerosis in grafted organs. It is currently unclear whether similar mechanisms could link the focal vascular inflammation seen in RA to distant atherosclerosis. However, endothelial cell dysfunction (ECD), commonly regarded as the first step in atherogenesis, is found in RA.[13] The mechanisms for

this are difficult to elucidate in RA, where arthritis and systemic disease co-exist. We have therefore focussed our studies on primary systemic vasculitis (1^0SV) as a model where vascular inflammation occurs in the absence of arthritis.

EC DYSFUNCTION IN 1^0SV

ECD has been defined by experimental cardiologists as reduced responses to physiological stresses such as flow, which depend on endothelial cell production of NO. Testing for this is currently moving from the purely experimental into clinical laboratories, using several well established protocols. This useful tool has recently been applied to look at a variety of rheumatic disease.[14] In Birmingham, we first asked whether ECD occurred in 10SV, applying brachial artery flow-mediated vasodilatation to a small series of unselected patients. This showed for the first time that these responses are significantly lower than normals controls, with some patients showing no response or even inappropriate vaso-constriction.[15] A subsequent larger series confirmed that ECD occurs frequently in 1^0SV, independent of the precise category of vasculitis or the presence of auto-antibodies such as ANCA.[16] This has been confirmed by others, using a different methadology.[17] That study also found a link to disease activity.

The studies of endothelial function provide explanations for the some of the general malaise and vasomotor instability seen in active vasculitis. They also relate to the enhanced rate of CVS events seen in young adults who suffered Kawasaki syndrome in childhood. More speculatively, they may be an important contributor to the continuing relapse rate and late mortality in 1^0SV. The next challenge therefore is to understand the mechanisms linking vascular inflammation to ECD.

MECHANISMS FOR ECD INDUCTION IN SV

Our research indicates that the sphingolipid cascade activated by TNFα plays a key role in the induction of ECD. Inflammatory cytokines such as TNFα, well defined as key players in RA, are also important in 1^0SV. TNFα has direct effects on endothelium – but is usually seen as activating EC (up-regulating adhesion molecule expression in inflammation) rather than down-regulating it. The main feature of endothelial dysfunction is depression of nitric oxide (NO), the vasodilator released by the action of eNOS, the EC specific form of constitutive NO synthetase. We have established that TNFα can depress Ca signalling

in T-cells and can thus depress as well as activate T-cells. The mechanism has recently been defined as release of the sphingolipid signalling cascade via sphingomyelinase (SMase).[18]

eNOS activation is also Ca dependant - and EC are a rich source of SMase. Our current research demonstrates that SMase depresses EC production of NO in aortic patches as well as HUVEC. This again relates to depression of Ca^{2+} influx. The in-vivo relevance of these observations was established by demonstrating that SMase infusion in intact rats depresses blood flow responses to standard agonists such as ACh. Our current model for the ECD seen in vasculitis suggests that high local concentrations of TNF in vascular inflammation induce both local direct activation of EC by TNF plus release of soluble SMase into the bloodstream. This sSMase leads to distal ECD produced by the ceramide it produces from sphingosine in the membrane of distal EC. It is doubtful if TNF released from synovitis achieves sufficient concentration in the bloodstream to achieve this.

CVS DISEASE IN 10SV AND A MODEL FOR ATHEROSCLEROSIS IN RA

The finding of EC dysfunction suggests enhanced atherosclerosis should also be seen in 1^0SV. When specifically looked for, we found increases in both sub-clinical disease and clinical events in a series of patients with Wegeners.[19] The carotid involvement has been independently confirmed.[20] These factors are all consistent with our up-dated hypothesis that vascular inflammation is a key factor in the initiation of atherosclerosis in RA through the induction of endothelial dysfunction. RA is a chronic persistent disease with multiple abnormalities in metabolic profile and lifestyle. These may all be involved together with ECD in the enhanced rate of CVS disease seen in RA. EC dysfunction has been dramatically described as "the birth place of the plaque". Injured or dysfunctional EC can provide a substrate for the deposition of altered lipids and adhesion of monocytes that eventually lead to atheromatous plaque formation. They are less able to cope with the metabolic effects of stress and diminished physical activity so commonly seen in RA. ECD has been shown to be predictive of subsequent clinical events in idiopathic CAD and may also have a direct role in their induction. The inappropriate vasospasm seen in brachial artery responses can occur also in the coronary vessels. We speculate that this may be an important factor in those cases of SLE where early CAD in younger women can occur in the absence of obvious coronary artery narrowing.

CONCLUSION

RA has enhanced mortality rates predominantly due to CAD. This is particularly seen in sero-positive RA with extra-articular features. We have proposed that this relates to vascular inflammation and have shown that such vascular involvement may initiate EC dysfunction and thus fire off the accelerated atherosclerosis of RA. Research into the mechanisms has revealed that TNF produced in local vascular inflammation can release sphingolipid mediators directly into the bloodstream. These in turn can induce diffuse EC dysfunction and initiate atherosclerosis. TNF blockade should thus be beneficial – and indeed has been associated with improved EC function. The rheumatic diseases provide an ideal setting to investigate the links between inflammation and atherosclerosis, seen as of major importance in primary atherosclerosis, the major killing disease world-wide.

REFERENCE LIST

1. Kitas GD, Erb N. Tackling ischaemic heart disease in rheumatoid arthritis. Rheumatology (Oxford) 2003; 42(5):607-613.

2. Manzi S, WASKO MC, MANZI SUSA. Inflammation-mediated rheumatic diseases and atherosclerosis. Ann Rheum Dis 2000; 59(5):321-325.

3. 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(6): 407-413.

4. Goodson NJ, Wiles NJ, Lunt M, Barret EM, Silman AJ, Symmons DPM. Mortality in early inflammatory polyarthritis: Cardiovascular mortality is increased in seropositive patients. Arthritis Rheum 2002; 46(8):2010-2019.

5. Kitas GD, Banks MJ, Bacon PA. Cardiac involvement in rheumatoid disease. Clin Med J Royal Coll Phys 2001; 1:18-21.

6. Mikuls TR, Saag KG, Criswell LA, Merlino LA, Kaslow RA, Shelton BJ et al. Mortality risk associated with rheumatoid arthritis in a prospective cohort of older women: results from the Iowa Women's Health Study. Ann Rheum Dis 2002; 61(11):994-999.

7. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003; 107(3):363-369.

8. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol 2002; 29(1):62-67.

9. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis Rheum 2002; 46(4): 862-873.

10. Bacon PA, Kitas GD. The significance of vascular inflammation in rheumatoid arthritis. Ann Rheum Dis 1994; 53:621-623.

11. Westedt ML, Meijer CJ, Vermeer BJ, Cats A, de Vries E. Rheumatoid arthritis–the clinical significance of histo- and immunopathological abnormalities in normal skin. J Rheumatol 1984; 11(4):448-453.

12. Turesson C, Jacobsson L, Bergstrom U. Extra-articular rheumatoid arthritis: prevalence and mortality. Rheumatology (Oxford) 1999; 38(7):668-674.

13. Van Doornum S, McColl G, Jenkins A, Green DJ, Wicks IP. Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function. Arthritis Rheum 2003; 48(1):72-80.

14. Bacon PA. Endothelial cell dysfunction in systemic vasculitis: new developments and therapeutic prospects. Curr Opin Rheumatol 2005; 17(1): 49-55.

15. Raza K, Thambyrajah J, Townend JN, Exley AR, Hortas C, Filer AD et al. Suppression of inflammation in primary systemic vasculitis restores vascular endothelial function: lessons for atherosclerotic disease? Circulation 2000; 102(13):1470-1472.

16. Filer AD, Gardner-Medwin JM, Thambyrajah J, Raza K, Carruthers DM, Stevens RJ et al. Diffuse endothelial dysfunction is common to ANCA associated systemic vasculitis and polyarteritis nodosa. Ann Rheum Dis 2003; 62(2):162-167.

17. Booth AD, Jayne DR, Kharbanda RK, McEniery CM, Mackenzie IS, Brown J et al. Infliximab improves endothelial dysfunction in systemic vasculitis: a model of vascular inflammation. Circulation 2004; 109(14):1718-1723.

18. Church LD, Hessler G, Goodall JE, Rider DA, Workman CJ, Vignali DAA et al. TNFR1-induced sphingomyelinase activation modulates TCR signalling by impairing store-operated Ca2+ flux. J Leukoc Biol. In press 2005.

19. Zaenker M, Aries PM, Herlyn K, Lamprecht P, Bacon PA, Gross WL. Accelerated Atherosclerosis in Wegener`s Granulomatosis (WG): A Sonographic Case-control Study on Intima Media Thickness. Arthritis Rheum 2002; 46(S1):185.

20. Leeuw K, Danders J, Stegeman C, Smit A, Kallenberg C, Bijl M. Accelerated atherosclerosis in Wegeners Granulomatosis. Arthritis Rheum 2004; 50(9 (S)):230.