Could antibodies to C-reactive protein link inflammation and cardiovascular disease in patients with systemic lupus erythematosus?

Sean G O’Neill, David A Isenberg, Anisur Rahman

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Most patients with SLE are young women who would normally be very unlikely to develop CVD. In women with SLE aged 35–44, the risk of CVD is up to 50 times that of age- and sex-matched controls. Several studies have examined the possible reasons for this increased risk. Although traditional risk factors such as hypertension, smoking and lipid levels contribute part of the increased risk, they do not explain all of it.

Atherosclerosis is an inflammatory condition. As SLE is characterised by inflammatory flares affecting different organs and tissues of the body, it has been suggested that these flares contribute to the development of atherosclerosis. SLE is also characterised by the presence of autoantibodies. Some of these can contribute to development of cardiovascular disease by promoting atherosclerosis. Antiphospholipid antibodies (APL), for example, promote arterial and venous thrombosis and activate endothelial cells. However, levels of APL have rarely been linked to disease activity in SLE patients, and a recent study in 200 patients with SLE showed that the prevalence of carotid artery plaques did not differ between APL-positive and APL-negative patients. Other antibodies could potentially exert a direct action on cardiac tissue. This is recognised in the foetal heart where anti-Ro antibodies crossing from the maternal circulation attack the conducting tissue to cause foetal heart block. However, it should be stressed that anti-Ro antibodies do not affect the adult heart and levels of anti-Ro do not reflect SLE disease activity.

Are there other autoantibodies that could link inflammatory disease activity and CVD in SLE? There are a number of possible candidates, including anti-high density lipoprotein’ and anti-apolipoprotein A-1. In this editorial, we discuss the possibility that anti-C-reactive protein (CRP) antibodies could also play such a role in this link.

CRP and anti-CRP in SLE

CRP, a marker of inflammation, is an independent predictor of CVD. This has been shown in large prospective studies in adults with no previous history of CVD. The predictive effect of raised CRP is moderate and the mechanism is not clearly understood. The study of CRP in animal models is complicated by the fact that CRP is only a trace protein in mice and neither mouse nor rat CRP fixes complement. Human CRP infused into mice or rats does fix complement, and such infusions enhanced the amount of cardiac infarction caused by ligation of the coronary artery in rats. This effect was abrogated by complement depletion. Vascular injury causes more thrombosis in mice transgenic for human CRP than in congenic wild-type mice. Apolipoprotein E-deficient mice that were transgenic for human CRP were reported to develop enhanced atherosclerosis compared to non-transgenic apolipoprotein E-deficient mice. Conversely, a second group found that the human CRP transgene exerted no such effect in these mice. In humans, it seems likely that CRP is deposited in ischaemic cardiac tissue, fixes complement and thus causes cardiac damage. In support of this, Lagrand et al carried out immunohistochemical studies of cardiac tissue obtained from autopsies of 17 patients who died after acute myocardial infarction and showed co-localisation of CRP and complement in infarcted but not healthy areas of myocardium. In blood vessels, CRP can bind to low density lipoprotein (LDL), altering its uptake into atherosclerotic plaques.

So could CRP itself be the link between disease activity and CVD in SLE? One problem with this hypothesis is that CRP levels are not highly elevated in flares of SLE, although large population studies do show links between CVD and CRP at levels below 10 mg/L. However, many of these studies assessed very few young women, so that their relevance to SLE could be limited. Another problem is the modest effect of raised CRP concentration. In the Reykjavik study, patients in the highest tertile of baseline CRP concentration had a 1.45 times higher risk of developing CVD than those in the lowest tertile. This could explain no more than a small proportion of the excess risk of CVD in SLE.

What about antibodies to CRP? These were first reported in patients with SLE by Bell et al in 1998. This finding has been confirmed by several groups who showed that anti-CRP antibodies are found in between 23% and 78% of patients with SLE, but occur very rarely in healthy controls. Reports from groups in Sweden and the USA show that anti-CRP levels do not correlate with serum CRP but might correlate with disease activity. In particular, anti-CRP levels rise during renal flares. In a recent study, Figueredo et al confirmed that patients with SLE and acute nephritis were more likely to have anti-CRP antibodies than those without nephritis, and also showed that anti-CRP antibodies were associated with increased risk of AP positivity, thrombosis and foetal loss.

Serum anti-CRP antibodies do not bind native pentameric CRP, but bind monomeric CRP (mCRP). Native CRP (nCRP) dissociates spontaneously into mCRP in vitro in the absence of calcium ions, but it is not clear whether mCRP exists in vivo. Some authors contend that mCRP is very unlikely to exist within the body, whereas others suggest that it is present in blood vessel walls. If the latter supposition is correct, then mCRP could exert biological effects on blood vessels. There is some evidence for this, but it is not clear whether mCRP promotes atherosclerosis or protects against it. In apolipoprotein E knockout mice, subcutaneous injections of nCRP enhanced development of atheroma whereas mCRP reduced it. Conversely, another study suggested that mCRP and nCRP have proatherogenic effects on human aortic endothelial cells in vitro. Free mCRP blocks complement activation whereas mCRP bound to oxidised or enzymatically modified LDL activates complement. This complement activation could clearly contribute to development of atheroma, especially as CRP and LDL levels are independent predictors of the development of CVD.

The fact that antibodies specific for mCRP, but not nCRP, exist in patients with SLE suggests strongly that mCRP

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must exist in these patients and that it acts as an antigen. The currently favoured explanation for development of autoantibodies in SLE proposes that apoptotic cell debris is not cleared efficiently by phagocytes in patients with SLE so that antigens on the surface of these cell fragments can act as immunogens. CRP is involved in the clearance of this material by phagocytes, and it has been proposed that under the acidic conditions prevalent in inflamed tissues mCRP could dissociate to form nCRP. Thus, mCRP on the surface of apoptotic cell fragments could be the driving antigen for production of anti-CRP in patients with SLE and this process could be enhanced during acute inflammatory flares of the disease. These ideas have been proposed particularly by Sjowall and colleagues, who have published a series of important papers on the subject of CRP and anti-CRP in SLE,13 21 22, which they have reviewed recently.11

Our hypothesis is therefore that disease activity and CVD in patients with SLE are linked by the production of anti-CRP antibodies that interact with mCRP in vascular tissue to promote the production of atherosclerosis. The hypothesis predicts that raised anti-CRP levels in patients with SLE could be an independent predictor of the development of CVD, even after adjusting for other risk factors.

HOW COULD INVESTIGATORS TEST FOR AN ASSOCIATION BETWEEN ANTI-CRP AND CVD IN PATIENTS WITH SLE?

Experiments in animal models would involve introducing human anti-CRP and human CRP into the animals, because mouse and rat CRP are functionally different to human CRP.13 It might be informative to carry out multi-centre studies with appropriate control groups (e.g. mice exposed to human CRP only, anti-CRP only or both) or to introduce human anti-CRP into mice transgenic for human CRP.13 However, this transgene is only expressed at high levels in male mice, which is problematic in trying to model SLE as it is a disease that occurs predominantly in women.

Human studies would involve testing anti-CRP levels in patients with SLE repeatedly to allow for the fact that these levels vary with disease activity. The patient group could be subdivided into tertiles according to mean anti-CRP level or into those who either had or had not experienced a rise in anti-CRP. Clinical outcomes in these subgroups would then be determined.

Studies looking at associations between serum measurements and the incidence of CVD events in cohorts of patients with SLE are difficult, because the overall number of CVD events in the cohort is invariably low even though the relative risk for CVD is high. Figueredo et al found that the presence of anti-CRP antibodies was associated with thrombosis/foetal loss in 137 patients with SLE, but the number of patients with arterial CVD was not reported. Many patients in multiple centres are needed to collect enough cases of arterial CVD to detect statistically significant associations.3 Studying large numbers of patients also enables investigators to carry out multi-variable analysis to identify independent risk factors for development of CVD.7

An alternative approach would be to study associations between anti-CRP antibody levels and sub-clinical surrogate markers of CVD, such as coronary artery calcification measured by electron beam tomography (EBT) or carotid plaque detected by ultrasound scanning.8 9 EBT and carotid ultrasound have shown cardiovascular abnormalities in patients with SLE, compared to age- and sex-matched controls. However, the predictive value of these measures for CVD in patients with SLE has not been established and the relationship between these sub-clinical cardiovascular abnormalities and inflammatory activity is not clear.

It might be necessary to carry out all three types of study: effects of anti-CRP in mice, prolonged multi-centre studies of CVD event rates in patients, and shorter human studies using surrogate markers of CVD. These studies are important because we do not know which patients would benefit from more aggressive treatment of inflammation in SLE by gaining better long-term cardiovascular outcome. It would be very useful to discover whether repeated measurements of anti-CRP could be used to help identify these patients.

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Authors’ affiliations
Sean G O’Neill, David A Isenberg, Anisur Rahman, Centre for Rheumatology, Division of Medicine, University College London, UK

Correspondence to: Dr Anisur Rahman, Reader in Rheumatology, Room 331, Windeyer Institute, 46 Cleveland Street, London W1T 4JF, anisur.rahman@ucl.ac.uk

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