

# The potential role of statins in the treatment of rheumatoid arthritis

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**ABSTRACT** Rheumatoid arthritis is characterised by uncontrolled chronic inflammation of the joints, which leads to their destruction and functional disability. It is also associated with increased and early cardiovascular mortality. This is thought to be linked to chronic systemic inflammation, which can lead to accelerated atherosclerosis, and thus earlier and more severe CHD. The beneficial effects of statins in the primary and secondary prevention of CHD are well-established. These are not only due to their lipid-lowering properties. Statins have several anti-inflammatory and immunomodulatory effects through which they may modify the inflammatory mechanisms involved in the generation and rupture of atherosclerotic plaques. These effects may also be useful for controlling rheumatoid inflammation. Thus statins may be an important adjunctive therapy in RA, aiming to both reduce joint inflammation and improve cardiovascular outcome. This needs to be tested in randomised controlled trials designed specifically for the purpose.

**KEYWORDS** Cardiovascular disease, inflammation, rheumatoid arthritis, statins.

**LIST OF ABBREVIATIONS** C-reactive protein (CRP), cardiovascular disease (CVD), cholesterol and recurrent events (CARE), class II transactivator (CIITA), cluster of differentiation (CD), congestive heart failure (CHF), coronary heart disease (CHD), disease activity score 28 (DAS28), disease-modifying anti-rheumatic drugs (DMARDs), endothelial cells (EC), erythrocyte sedimentation rate (ESR), farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP), heart protection study (HPS), high sensitivity CRP (hsCRP), human leukocyte antigen (HLA), hydroxy-methyl-glutaryl coenzyme A (HMG-CoA), inter-cellular adhesion molecule (ICAM), interferon gamma (IFN $\gamma$ ), interleukins (IL), lipopolysaccharide (LPS), low density lipoproteins (LDL), lymphocyte function antigen (LFA), major histocompatibility complex (MHC), myocardial infarction (MI), matrix metalloproteinases (MMPs), mevalonic acid (MVA), monocyte chemoattractant protein (MCP), myocardial infarction (MI), nuclear factor (NF), peroxisome proliferator-activated receptor-alpha (PPAR $\alpha$ ), rheumatoid arthritis (RA), scandinavian simvastatin survival study (4S), vascular smooth muscle cell (VSMC), T helper (Th), tumour necrosis factor alpha (TNF $\alpha$ ), West of Scotland coronary prevention study (WOSCOPS)

**DECLARATION OF INTERESTS** Doctors Kitas and Sattar have funding from Pfizer and have declared a non-personal interest.

## RHEUMATOID ARTHRITIS AND CARDIOVASCULAR DISEASE

Rheumatoid arthritis is the most common type of chronic inflammatory arthritis, affecting about 0.8% of the adult population in Britain.<sup>1</sup> Its cardinal clinical manifestations involve the joints, where chronic, uncontrolled inflammation leads to stiffness, swelling, pain, and eventually destruction of the normal joint architecture. Rheumatoid arthritis is also a systemic disease, as indicated by the presence of constitutional symptoms and multiple extra-articular features, including vasculitis. The disease remains incurable and has a poor long-term outcome, not only in terms of disability but also life expectancy, which is

shortened by 3 to 18 years.<sup>2</sup> Indeed, the mortality of severe RA is comparable to that of triple-vessel CHD or stage IV Hodgkin's lymphoma,<sup>3</sup> and has not improved much over the last three decades, despite significant treatment advances. Almost half of all deaths in RA (and about 35–40% of the excess deaths) are due to CVD. Most studies have found increased cardiovascular mortality (standardised mortality ratios of 1.13–5.25), with the lower estimates being for MI alone whereas the highest also include CHF.<sup>4,5</sup> The increased cardiovascular mortality of RA can only be due to either higher prevalence or greater case fatality of CVD, compared with the general population. Greater case fatality may be due to multiple reasons, including pathogenic differences

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(discussed in more detail below), but also different clinical presentation and management of CVD in patients with RA. Cardiovascular disease is a very common comorbidity in RA:<sup>6</sup> rheumatoid heart disease (e.g. pericarditis) is present in about 40% of patients on echocardiography or autopsy but rarely causes haemodynamic consequences, so it is considered an unlikely cause of death.<sup>7</sup> Instead, most cardiovascular deaths in RA are due to ischaemic pathologies, such as MI and CHF, which, in the general population, are mainly due to atherosclerotic involvement of the coronary arteries. Interestingly, although RA associates with a very significant load of classical atherosclerotic CHD risk factors (e.g. hypertension, dyslipidaemia),<sup>8-10</sup> this does not appear to explain the increase in ischaemic events.<sup>11</sup> This suggests that other mechanisms may be involved, and most of the interest has turned to chronic inflammation, the common denominator between the pathology of RA and atherosclerosis.

### CHRONIC INFLAMMATION IN RHEUMATOID ARTHRITIS

The main site of inflammation in RA is the synovial membrane (synovium). Rheumatoid synovium becomes a hyperplastic, highly vascularised tissue heavily infiltrated by chronic inflammatory cells. Rheumatoid arthritis is genetically linked to certain major histocompatibility complex class II antigens (HLA-DRB1\*0404 and 0401). Class II molecules present antigenic peptides to CD4<sup>+</sup> T cells, and this suggests that RA is caused by an, as yet unidentified, antigen. CD4<sup>+</sup> activated T lymphocytes are central to rheumatoid chronic synovitis. They can stimulate monocytes, macrophages and synovial fibroblasts to produce cytokines such as IL-1 and -6 and TNF $\alpha$ . Through cell-surface signalling (e.g. CD69 and CD11 or CD40 ligand and CD28) or through the release of specific cytokines (e.g. IFN $\gamma$ , IL-17 and others) they also regulate the secretion of MMPs and other effector molecules (e.g. free radicals) from macrophages and the stimulation of B cells to produce antibodies. Activated inflammatory cells and their products may have multiple effects. They can promote further inflammatory cell recruitment by activating EC to express adhesion molecules and by releasing chemokines such as IL-8: this could, in part, explain the flares and overall chronicity of the disease. They can stimulate neo-angiogenesis, which would explain the increased vascularity of the inflamed synovium. They may be involved in cartilage and bone degradation through multiple mechanisms including MMP and free radical release, and direct effects on osteoclasts and chondrocytes, which may explain the erosive damage to the joint.<sup>12</sup> The main inflammatory cytokines, IL-1, IL-6 and TNF $\alpha$ , also have important effects on distant organs, e.g. the liver, muscle, fat and vascular endothelium. These systemic effects explain several other phenomena, including the acute phase response (which is used for monitoring the inflammatory activity of RA in everyday

clinical practice), rheumatoid cachexia (the loss of lean body mass),<sup>13</sup> and a constellation of effects, which may collectively promote atherogenesis (e.g. dyslipidaemia, insulin resistance, thrombogenesis, and endothelial dysfunction amongst others).<sup>5,14</sup> It is interesting that the extent of inflammatory activity in RA, assessed by the acute phase response (e.g. ESR or CRP), clinical measures (e.g. joint swelling) or indices combining both, associates not only with the extent of joint damage and disability, but also with cardiovascular events and death.<sup>15-19</sup> Effective control of inflammatory activity using DMARDs, may, in contrast, confer functional and survival benefits,<sup>20-24</sup> but there may be significant differences between individual drugs, requiring further investigation.

### INFLAMMATION IN ATHEROSCLEROSIS

The initiating step in atherosclerosis is thought to be endothelial cell dysfunction. The endothelium regulates cellular interaction with the vessel wall, controls coagulation, vascular tone and VSMC proliferation. Dysfunctional endothelium becomes procoagulant and proinflammatory.<sup>25</sup> Monocytes recruited locally, ingest lipid, become macrophages and eventually form foam cells, which initiate the formation of fatty streaks. This situation is perpetuated by local and systemic factors, leading to the formation of more advanced plaques. Inflammatory mechanisms are central to the development and instability/rupture of atherosclerotic plaques.<sup>26</sup> The cellular infiltrate, cytokine milieu, adhesion molecule expression and effector molecules found in the advanced plaque are very reminiscent of those found in the rheumatoid synovium, while systemic inflammation appears to associate with the outcome of CHD in the general population.<sup>27-29</sup> Locally, macrophages may act as antigen-presenting cells to CD4<sup>+</sup> T cells. As in the case of RA, these antigen(s) remain elusive, but candidates include oxidised or otherwise modified LDL, heat shock proteins or infective organisms. The chemokine MCP-1 is expressed in all stages of atherosclerosis<sup>30-32</sup> promoting local recruitment of monocytes and T cells. Most lesional T cells are activated CD4<sup>+</sup> Th1 type lymphocytes,<sup>33</sup> secreting cytokines such as IFN $\gamma$ , IL-2 and TNF- $\alpha$ , which can activate endothelium and macrophages. Endothelial activation, with the accompanying expression of adhesion molecules and release of soluble mediators, propagates further immune cell recruitment in the lesion, and induces prothrombotic and adhesive changes to the vasculature. TNF $\alpha$  and IL-1 promote VSMC proliferation, an important step in the formation of the atheromatous plaque, whereas T cell-derived IFN $\gamma$  can inhibit VSMC proliferation and reduce their collagen synthesis,<sup>34,35</sup> limiting the strength of the fibrous cap and leading to an unstable plaque. Matrix metalloproteinase and free radical release by activated macrophages can degrade collagen and further weaken the plaque structure. It is obvious that there are many similarities between the inflammatory mechanisms involved in rheumatoid synovitis and joint damage described in the

previous section and those involved in the formation and rupture of the atherosclerotic plaque described here.

Markers of systemic inflammation are closely linked with the development and outcome of atherosclerosis and CHD. Pathways involving systemic (rather than local) inflammation, may be particularly relevant to conditions such as RA, but it remains unclear whether they are of pathogenic importance or are epiphenomena (i.e. surrogate markers of other underlying processes). The best characterised is the acute phase protein CRP, but fibrinogen, the white cell count, circulating IL-1, TNF $\alpha$ , and soluble adhesion molecules (amongst others) have also been linked. C-reactive protein rises significantly in response to inflammatory stimuli predominantly under transcriptional control from IL-6. In several studies, the application of hsCRP assays in patients with CHD, as well as recent meta-analyses confirm a predictive ability of CRP (and to a lesser extent other circulating markers of inflammation) for future coronary events.<sup>36–40</sup> 'High' baseline hsCRP values are mostly within the normal range (using routine assays), suggesting that low-grade systemic inflammation is sufficient for the potentiation of atheromatous CHD. This may be just an epiphenomenon, reflecting the local inflammatory response in atherosclerotic plaques or other low-grade inflammatory stimuli in the body, or it may reflect adiposity, since adipocytes are a major source of IL-6 secretion and the Body Mass Index correlates with CRP levels.<sup>39</sup> Alternatively, systemic inflammation may be of pathogenic importance, since it can be linked to multiple CHD risk factors including endothelial dysfunction, dyslipidaemia and LDL modification, insulin resistance and dysregulated coagulation.<sup>14</sup>

## CHD, INFLAMMATION AND STATINS

A number of large, international, multi-centre trials have clearly demonstrated the beneficial impact of statin therapy in CHD. For example, the 4S,<sup>41</sup> the WOSCOPS,<sup>42</sup> the CARE trial<sup>43</sup> and the HPS<sup>44</sup> have clearly and unequivocally shown that statin therapy is highly beneficial in reducing the risk of vascular disease. On average, the risk for vascular end-points is reduced by around 25–40% by statins. What is more remarkable is that such benefits have been documented in subjects with or without existing vascular disease, with and without diabetes, and generally irrespective of the starting cholesterol concentration, age or gender. Indeed, their impact in atherogenesis prevention has been so dramatic that some researchers have drawn comparisons to the impact of penicillin in treating infectious diseases.<sup>45</sup> From these studies came firm new evidence on which to base our current clinical practice. The primary mechanism of action shared by all statins is up-regulation of the LDL-receptor and enhanced clearance of LDL and other apolipoprotein B containing lipoproteins from the plasma. They also tend to lower triglyceride concentrations and variably increase

HDL-cholesterol concentrations. However, close scrutiny of the trial results raises the issue of whether the unexpectedly rapid onset of such striking clinical benefits can be attributed to cholesterol reduction alone.<sup>46</sup> Laboratory and clinical evidence is certainly accumulating to the effect that individual statins may possess benefits beyond their cholesterol lowering capability, particularly with regard to anti-inflammatory properties. Effects have also been reported on other pathways including plaque stabilisation, restoration of endothelial function, protection against lipoprotein oxidation and effects on rheological factors and blood coagulation.<sup>46</sup> These are collectively referred to as 'pleiotropic effects of statins' and are summarised in Table I. Statin therapy impacts upon many of these processes, helping to reduce the likelihood of atherosclerotic plaque rupture, or limiting thrombus formation should rupture occur. Recent evidence indicates that this may result from a reduction in the number of inflammatory cells within the plaque<sup>47</sup> and as a result, change in plaque composition and architecture, leading to the development of a stiffer, more stable lesion.<sup>48</sup> Whether such statin-mediated anti-inflammatory effects are merely secondary to their lipid-lowering actions rather than direct anti-inflammatory effects remains to be clarified. An interesting hypothesis has recently been proposed, in which the lipid-modulating properties of statins are split in two categories: reduction of serum lipid levels (which may be, to a large extent, independent of inflammation) and disruption of lipid rafts (cholesterol-rich areas of the cell membranes), which may be intimately involved in immune cell activation (and thus the inflammatory response). It remains unknown whether serum and membrane cholesterol are differentially affected by statins, and whether different statins have a different degree of effect in these pathways.<sup>50</sup>

### Statins and immunosuppression

In the late 1980s, experiments demonstrated an obligatory requirement for mevalonic acid (but not cholesterol) in order to facilitate the cytolytic activity characteristic of natural killer cells.<sup>51</sup> Statins were then shown, in pharmacological doses, to inhibit lymphocyte proliferation *in vitro* and block their cytolytic actions.<sup>52</sup> These findings were, however, largely forgotten until they were re-discovered by Kobashigawa and his colleagues.<sup>53</sup> In a prospective randomised trial of pravastatin therapy administered to heart transplant recipients they assessed whether transplant vasculopathy, associated with raised plasma lipid levels, could be avoided. Serendipitously, they discovered that episodes of acute graft rejection were reduced and, in consequence, graft survival prolonged. They pursued this line of investigation with a second study that demonstrated prolongation of kidney graft survival following pravastatin treatment. They proposed several possible explanations for these intriguing findings, including reduction in natural killer T-cell cytotoxicity, enhancement of immunosuppression due to synergism between pravastatin and the immunosuppressant drug,

TABLE 1 Pleiotropic effects of statins.

Process	Increase	Decrease
<b>Oxidative stress</b>	Natural antioxidants (Vitamins C and E, Glutathione)	ox-LDL generation and uptake superoxide generation (Rho inhibition)
<b>Inflammation and immunoregulation</b>		
<b>Leukocytes</b>		PMN infiltration (foot-pad oedema) MCP-1 production and leucocyte migration (air-pouch) Leukocyte rolling, adhesion and transmigration (normocholesterolaemic rat) Suppressed Th1 humoral and cellular responses (collagen-induced arthritis) EAE Adhesion molecule upregulation Cytokine and chemokine release by leukocytes MHC class II expression by APCs LFA-1/ICAM-1 interaction
<b>Endothelial cells</b>	eNOS expression/stability eNOS-calmodulin interaction Bone marrow-derived EC progenitors TPA expression PK Akt, so promotion of angiogenesis	PAI-1 expression COX-2 expression Lipoxygenase products Endothelin-1 expression and synthesis Adhesion molecule expression (e.g. P-selectin) MHC Class II
<b>VSMC</b>	Apoptosis Myosin protein phosphatase Na <sup>+</sup> pump activity, so reduced [Ca <sup>++</sup> ] <sub>i</sub>	NADH oxidase activity, so less ROS Proliferation, migration TF expression/activity Contractility responses
<b>Coagulation</b>		Fibrinogen Thrombin generation Macrophage-derived TF Blood viscosity Platelet aggregation Platelet/EC adhesion Thromboxane A2

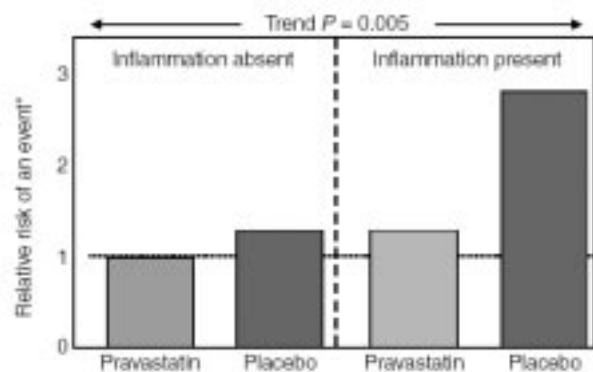
cyclosporin, and simple lowering of plasma lipid levels. They did point out, in partial dismissal of the latter, that the immunosuppressive action was apparently independent of the degree of cholesterol lowering achieved.

### Statins, CRP and risk for CHD

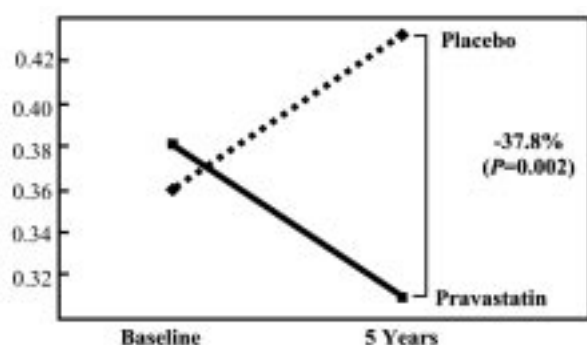
The above data stimulated researchers to ask whether the potential anti-inflammatory effects of statins may also play an important role in the cardioprotective action of

these drugs. As noted above, histological examinations of atherosclerotic lesions reveal the presence of inflammatory cells, together with newly formed as well as disintegrating fibrous tissue.<sup>54</sup> If statins had innate anti-inflammatory properties, they would then be able to impact directly on the stability of the plaques.

Initial *ex vivo* observations suggested that pravastatin had the ability to reduce LPS-induced IL-6 and TNF $\alpha$  release from macrophages.<sup>55</sup> Subsequently, several *in vivo* studies



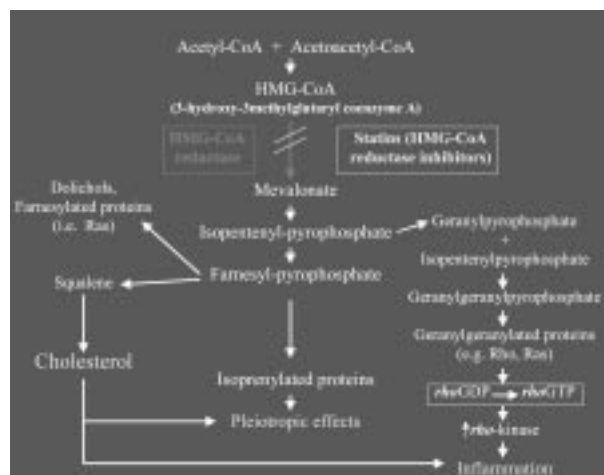
**FIGURE 1** Effect of pravastatin on plasma CRP levels in the CARE study. Data from Ridker *et al.* 1999.



**FIGURE 2** Inflammation, pravastatin, and relative risk of recurrent coronary events: subgroup analysis from Cholesterol and Recurrent Events trial. Recurrent myocardial infarction or death from coronary heart disease. Data from Ridker *et al.* 1998.

showed that all statin drugs reduce circulating CRP concentrations and do so by near equivalent amounts<sup>56–58</sup> (see figure 1 for example). Interestingly, all such studies suggest no correlation between the extent of LDL-cholesterol reduction and decline in CRP. Additionally, administration of pravastatin in CARE was associated with a minor risk reduction in patients in whom CRP levels was low at baseline, but a marked risk reduction in those with elevated CRP levels, even though the degree of reduction in LDL-cholesterol was directly comparable in both groups (See figure 2). These results suggest not only that those patients who had a high CRP (and therefore a pro-inflammatory status at the beginning of the study) are more likely to benefit from statin therapy, but also that statin therapy reduces the levels of CRP. Recent re-analysis of the PROVE IT-TIMI 22 trial has also shown that patients who achieve low CRP levels as a result of statin therapy have better clinical outcomes than those with higher CRP levels, irrespective of the resultant level of LDL cholesterol.<sup>59</sup>

Elaborating the mechanisms whereby statins impact upon inflammatory pathways and in particular whether such effects are independent of their lipid-lowering actions has assumed considerable importance. A number of recent observations have begun to unravel responsible mechanisms.



**FIGURE 3** Biochemical pathways mediating the lipid-lowering, anti-inflammatory and pleiotropic effects of statins.

### Molecular mechanisms for statin anti-inflammatory effects

Hydroxy-methyl-glutaryl coenzyme A reductase catalyses the conversion of HMG-CoA to MVA during cholesterol synthesis (See figure 3). Downstream metabolites, including GGPP and FPP regulate prenylation within several critical signalling pathways<sup>60</sup> and one indirect effect of GGPP modulation by statins is activation of PPAR $\alpha$ .<sup>61</sup> This latter effect may explain both the HDL-cholesterol raising property of statins<sup>41–44</sup> and their anti-inflammatory effects since PPAR $\alpha$  activation leads to inhibition of inflammatory pathways. Indeed, statin-induced changes in serum CRP concentrations have been inversely associated with changes in HDL-cholesterol but not, as noted before, to LDL-cholesterol.<sup>62</sup> Peroxisome proliferator-activated receptor-alpha activation leads to an inhibition of a range of inflammatory response genes by negatively interfering with NF-kappa  $\beta$  and AP-1 signalling pathways; an ability of atorvastatin to reduce NF-kappa  $\beta$  activation in vascular smooth muscle cells and mononuclear cells has been noted.<sup>63</sup> Nevertheless, the above mechanisms appear to explain previous observations demonstrating ability of statins to reduce the production of IL-1 $\beta$ , IL-6, TNF $\alpha$ , cyclooxygenase-2, MCP-1 by a variety of cell types.<sup>64–66</sup>

Statins may inhibit IFN $\gamma$ -inducible macrophage MHC class II expression via CIITA suppression.<sup>67</sup> This novel observation is relevant since MHC class II molecules are directly involved in the activation of T lymphocytes and in the control of the immune response. Some statins (lovastatin, simvastatin) may modulate T cell co-stimulation through direct effects on LFA-1/ICAM-1 interactions, dependent upon recognition of a novel statin binding site on  $\beta$ 2 integrins.<sup>68</sup> These properties indicate that statins might modulate functional maturation of T lymphocytes, which, as mentioned, are the central orchestrators of the inflammatory response both in the atherosclerotic plaque and the rheumatoid synovium. Some of the sources of evidence for the anti-inflammatory effects of statins are summarised in Table 2.

**TABLE 2** Summary of evidence for anti-inflammatory effects of statins.

Source of data	Findings
<i>Clinical</i>	Reduction in incidence of organ transplant rejection Modification of plaque composition – reduced inflammatory cells, reduced LDL oxidation Reduction in CRP concentrations unrelated to LDL-cholesterol reduction Benefit from statin therapy related to baseline CRP concentration Improvement in endothelial function correlated to CRP reduction Reduced disease activity and inflammatory markers in RA with statin relative to placebo
<i>Animal data</i>	Prevention of carageenan-induced foot-pad oedema Prevention or delay in collagen-induced arthritis Modification of plaque composition – reduced inflammatory cells, reduced calcification and neovascularisation.
<i>Ex vivo/in vitro data</i>	Reduction in LPS-induced macrophage release of pro-inflammatory mediators such as IL1 $\beta$ , IL-6, TNF- $\alpha$ , MCP-1 Similar data for endothelial cells Stimulation of eNOS release from endothelial cells
<i>Mechanistic</i>	Modulation of critical signalling pathways via effects on GGPP and FPP PPAR $\alpha$ activation NFkappa- $\beta$ inhibition via Ikappa $\beta$ activation Inhibition of IFN $\gamma$ -inducible MHC class II expression Binding to $\beta$ 2 integrins to prevent T cell co-stimulation through direct effects on LFA-1/ICAM-1 interactions

## WHERE NEXT?

Despite the wealth of the above observations, many researchers remain sceptical about the 'apparent' anti-inflammatory effects of statins, pointing out, for example, that statin-induced CRP reductions may be a consequence of reduced hepatic CRP synthesis rather than necessarily any effects on 'upstream' cytokine networks.<sup>69</sup> Nevertheless, the consistency of many different studies, and in particular effects of statins on cells of the immune system, prompted researchers to test whether these drugs offer clinically apparent anti-inflammatory effects independently of cholesterol reduction or in the context of auto-immune diseases characterised by high grade inflammation. Such studies are now beginning to emerge and provide a more robust test of statin anti-inflammatory potential.

A very recent study in the cardiovascular field showed that reduction of the inflammatory component of CVD through statin therapy improved the clinical outcome irrespective of the reduction of serum cholesterol. Patients with angiographically proven CHD were randomised to receive either moderate statin therapy (pravastatin 40 mg od) or intensive statin therapy (atorvastatin 80 mg od). Progression of atherosclerotic

disease was assessed using intravascular ultrasound at baseline and 18 months later, while lipoprotein and CRP levels were monitored. There was a reduced rate of atherosclerosis progression with intensive statin therapy compared to the moderate therapy group. This was significantly related to greater reductions in the levels of CRP, independently of reductions in lipoprotein levels.<sup>70</sup> In the re-analysis of the data of the PROVE IT-TIMI 22 trial mentioned above<sup>59</sup> Ridker and colleagues showed that those patients who show lower CRP levels as a result of statin therapy have a better outcome than those whose CRP remains higher, irrespective of the levels of serum cholesterol achieved through taking the statin. Such results appear to clearly dissociate the clinical effects arising from cholesterol reduction from those arising from control of inflammation through statin therapy. The question is whether such effects could be observed in disease states characterised by 'high grade' inflammatory activity.

Rheumatoid arthritis is probably the best disease model in which to study this. In a proof-of-concept, randomised, double-blind, placebo controlled trial, McCarey and colleagues used atorvastatin 40 mg once daily vs placebo as adjunct therapy in 116 RA patients receiving DMARDs.<sup>71</sup> The patients were followed up for six months and were

assessed for changes in vascular risk factors (e.g. lipids, fibrinogen) and disease activity (using IL-6, the acute phase response indices ESR and CRP, and the composite DAS28, which incorporates the ESR (or CRP), a swollen joint count based on the objective assessment of 28 joints and a subjective assessment of overall well-being performed by the patient on a 10 cm visual analogue scale). A DAS28 response occurred in significantly more patients on atorvastatin (30%) than placebo (10%). Relative to placebo, there was significantly more reduction of most serum and clinical markers of inflammation in the atorvastatin group, including the ESR, CRP, IL-6, and joint count. Low density lipoproteins were significantly reduced in the statin group. Even though the effects of statin therapy were quite modest (by rheumatological standards), this trial provides evidence that statins have the potential to modify the inflammatory response even in disease states characterised by high-grade inflammation. Similar results may soon formally emerge from other clinical entities, including multiple sclerosis and systemic lupus erythematosus.

The evidence for a link between rheumatoid inflammation and premature atherosclerosis<sup>72</sup> together with those for anti-inflammatory and immunomodulatory effects of

statins, makes this class of drugs particularly interesting as adjuvant therapy in RA. Whereas the results from initial clinical trials such as those mentioned above appear promising, they only emphasise the need for more definitive research in this field. It is important for example to find out whether the possible anti-inflammatory benefit of statins is sustained beyond six months. It is even more important to know whether the modest improvement in surrogate markers of inflammation does in fact translate into longer term improvement of hard end-points in RA, such as reductions in cardiovascular mortality, joint damage and physical disability. This requires further investigation in definitive, long-term, prospective trials designed specifically for the purpose.

## ACKNOWLEDGMENTS

The authors wish to thank their staff and collaborators, as well as the funding bodies that have supported their work in this field. The latter include the Arthritis Research Campaign, British Heart Foundation, Chief Scientist Office, Scotland, Dudley Group of Hospitals Research and Development Directorate and the Droitwich Medical Trust.

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