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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 (IFNγ), 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), monocyre chemotactic protein (MCP), myocardial infarction (MI), nuclear factor (NF), peroxisome proliferator-activated receptor-alpha (PPARα), rheumatoid arthritis (RA), scandinavian simvastatin survival study (4S), vascular smooth muscle cell (VSMC), T helper (Th), tumour necrosis factor alpha (TNFα), West of Scotland coronary prevention study (WOSCOPS)

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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.[1] 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.[2] Indeed, the mortality of severe RA is comparable to that of triple-vessel CHD or stage IV Hodgkin's lymphoma,[3] 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.[4,5] 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

(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:[6] 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.[7] 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),[8–10] this does not appear to explain the increase in ischaemic events.[11] 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 $CD4^+$ T cells, and this suggests that RA is caused by an, as yet unidentified, antigen. $CD4^+$ 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 TNFα. Through cell-surface signalling (e.g. CD69 and CD11 or CD40 ligand and CD28) or through the release of specific cytokines (e.g. IFNγ, 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.[12] The main inflammatory cytokines, IL-1, IL-6 and TNFα, 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),[13] and a constellation of effects, which may collectively promote atherogenesis (e.g. dyslipidaemia, insulin resistance, thrombogenesis, and endothelial dysfunction amongst others).[5,14] 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.[15–19] Effective control of inflammatory activity using DMARDs, may, in contrast, confer functional and survival benefits,[20–24] 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.[25] 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.[26] 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.[27–29] Locally, macrophages may act as antigen-presenting cells to $CD4^+$ 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[30–32] promoting local recruitment of monocytes and T cells. Most lesional T cells are activated $CD4^+$ Th1 type lymphocytes,[33] secreting cytokines such as IFNγ, IL-2 and TNF-α, 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. TNFα and IL-1 promote VSMC proliferation, an important step in the formation of the atheromatous plaque, whereas T cell-derived IFNγ can inhibit VSMC proliferation and reduce their collagen synthesis,[34,35] 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

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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, TNFα, 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.[36–40] '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 adipocity, since adipocytes are a major source of IL-6 secretion and the Body Mass Index correlates with CRP levels.[39] 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.[14]

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,[41] the WOSCOPS,[42] the CARE trial[43] and the HPS[44] 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.[45] 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.[46] 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.[46] These are collectively referred to as 'pleiotropic effects of statins' and are summarised in Table 1. 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[47] and as a result, change in plaque composition and architecture, leading to the development of a stiffer, more stable lesion.[48, 49] 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.[50]

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.[51] Statins were then shown, in pharmacological doses, to inhibit lymphocyte proliferation *in vitro* and block their cytolytic actions.[52] These findings were, however, largely forgotten until they were re-discovered by Kobashigawa and his colleagues.[53] 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
Oxidative stress	Natural antioxidants (Vitamins C and E, Glutathione)	ox-LDL generation and uptake superoxide generation (Rho inhibition)
Inflammation and immunoregulation		
Leukocytes		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
Endothelial cells	eNOS expression/stability	PAI-1 expression
	eNOS-calmodulin interaction	COX-2 expression
	Bone marrow-derived EC progenitors	Lipoxygenase products
	TPA expression	Endothelin-1 expression and synthesis
	PK Akt, so promotion of angiogenesis	Adhesion molecule expression (e.g. P-selectin)
		MHC Class II
VSMC	Apoptosis	NADH oxidase activity, so less ROS
	Myosin protein phosphatase	Proliferation, migration
	Na+ pump activity, so reduced [Ca++]I	TF expression/activity
		Contractility responses
Coagulation		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.[54] 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 TNFα release from macrophages.[55] Subsequently, several *in vivo* studies

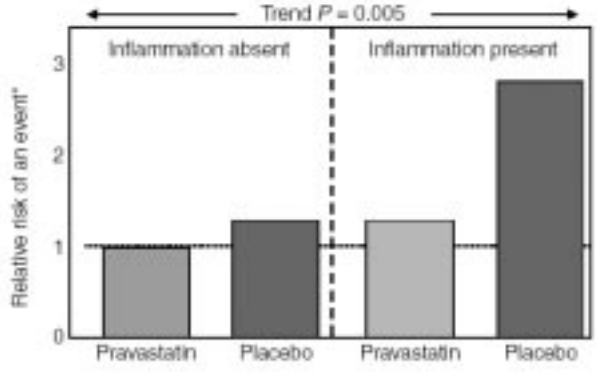

FIGURE 1 Effect of pravastatin on plasma CRP levels in the CARE study. Data from Ridker *et al.* 1999.

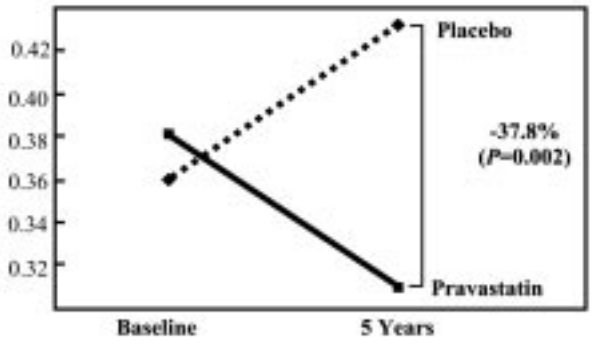

FIGURE 2 Inflammation, pravastatin, and relative risk of recurrent coronary events: subgroup analysis from Cholesterol and Recurrent Events trial. Recurrent myocardial infarction or death from coronary heart disease. Data from Ridker *et al.* 1998.

showed that all statin drugs reduce circulating CRP concentrations and do so by near equivalent amounts[56–58] (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.[59]

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.

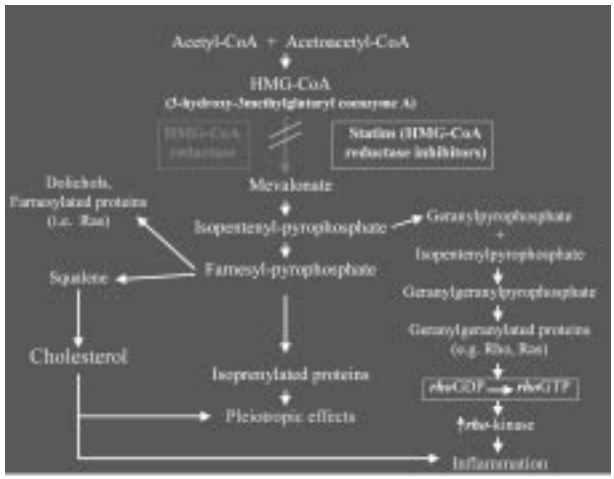

FIGURE 3 Biochemical pathways mediating the lipid-lowering, anti-inflammatory and pleiotropic effects of statins.

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[60] and one indirect effect of GGPP modulation by statins is activation of PPARα.[61] This latter effect may explain both the HDL-cholesterol raising property of statins[41–44] and their anti-inflammatory effects since PPARα 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.[62] Peroxisome proliferator-activated receptor-alpha activation leads to an inhibition of a range of inflammatory response genes by negatively interfering with NF-kappa β and AP-1 signalling pathways; an ability of atorvastatin to reduce NF-kappa β activation in vascular smooth muscle cells and mononuclear cells has been noted.[63] Nevertheless, the above mechanisms appear to explain previous observations demonstrating ability of statins to reduce the production of IL-1β, IL-6, TNFα, cycloxygenase-2, MCP-1 by a variety of cell types.[64–66]

Statins may inhibit IFNγ-inducible macrophage MHC class II expression via CIITA suppression.[67] 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 β2 integrins.[68] 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
Clinical	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
Animal data	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.
Ex vivo/in vitro *data*	Reduction in LPS-induced macrophage release of pro-inflammatory mediators such as IL1β, IL-6, TNF-α, MCP-1
	Similar data for endothelial cells
	Stimulation of eNOS release from endothelial cells
Mechanistic	Modulation of critical signalling pathways via effects on GGPP and FPP
	PPARα activation
	NFkappa-β inhibition via Ikappa β activation
	Inhibition of IFNγ-inducible MHC class II expression
	Binding to β2 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.[69] 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.[70] In the re-analysis of the data of the PROVE IT-TIMI 22 trial mentioned above[59] 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.[71] 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[72] 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.

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REFERENCES

1 Symmons DP, Turner G, Webb R *et al.* The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology* 2002; **41:**793–800.

2 Scott DL, Symmons DPM, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987; **1:**1108–11.

3 Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously: predictive markers, socioeconomic status and comorbidity. *J Rheumatol* 1986; **13:**841–5.

4 Goodson N. Coronary artery disease and rheumatoid arthritis. *Curr Opin Rheumatol* 2002; **14:**115–120.

5 Kitas GD, Erb N. Tackling ischaemic heart disease in rheumatoid arthritis. *Rheumatology* 2003; **42:**607–13.

6 Kroot EJJA, van Gestel AM, Swinkels HL *et al.* Chronic comorbidity in patients with early rheumatoid arthritis: a descriptive study. *J Rheumatol* 2001; **28:**1511–7.

7 Kitas GD, Banks MJ, Bacon PA. Cardiac involvement in rheumatoid disease. *Clin Med* 2001; **1:**18–21.

8 McEntegart A, Capell HA, Madhok R, Lowe GDO, Rumley A, Woodward M. Cardiovascular (CVS) Risk factors in an RA population. *Rheumatology* 2000; **39:**40.

9 Erb N, Pace AV, Douglas KJM, Banks M, Kitas GD. Risk assessment for coronary heart disease in rheumatoid arthritis and osteoarthritis. *Scand J Rheumatol* 2004; **33:**293–9.

10 Situnayake RD, Kitas GD. Dyslipidaemia and rheumatoid arthritis. *Ann Rheum Dis* 1997; **56:**341–2.

11 del Rincon ID, Williams K, Stern MP *et al.* High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; **44:**2737–45.

12 Choy EHS, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Eng J Med* 344; **12:**907–16.

13 Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. *Rheumatology* 2004; **43(10):**1219–23.

14 Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how 'high-grade' systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003; **108(24):**2957–63.

15 Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis: a retrospective cohort study from disease onset. *J Rheumatol* 1999; **26:**2562–71.

16 Pincus T, Callahan LF. Rheumatology function tests: grip strength, walking time, button test and questionnaires document predict longterm morbidity and mortality in rheumatoid arthritis. *J Rheumatol* 1992; **19:**1051–7.

17 Jacobsson LT, Turesson C, Hanson RL *et al.* Joint swelling as a predictor of death from cardiovascular disease in a population study of Pima Indians. Arthritis Rheum 2001; **44:**1170–6.

18 Chehata JC, Hassell AB, Clarke SA *et al.* Mortality in rheumatoid arthritis: relation to single and composite measures of disease activity. *Rheumatology* 2001; **40:**447–52.

19 Pincus T, Callahan LF, Sale WG *et al.* Severe functional declines, work disability and increased mortality in 75 rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984; **27:**864–72.

20 Wallberg-Jonsson S, Ohman ML, Rantapaa-Dahlqvist S. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol* 1997; **24:**445–51.

21 Choi HK, Herman MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; **359:**1173–7.

22 Mitchell DM, Spitz PW, Young DY, Bloch DA, McShane DJ, Fries JF. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986; **29:**706–14.

23 Lehtinen K, Isomaki H. Intramuscular gold therapy is associated with long survival in patients with rheumatoid arthritis. *J Rheumatol* 1991; **18:**524–9.

24 Krause D, Schleusser B, Herborn G, Rau R. Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. *Arthritis Rheum* 2000; **43:**14–21.

25 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):**1–17.

26 Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; **340:**115–27.

27 Kitas GD, Banks MJ, Bacon PA. Accelerated atherosclerosis as a cause of cardiovascular death in RA. *Pathogenesis* 1998; **1(2):**73–83.
28 Danesh J, Whincup P, Walker M, Lennon L *et al.* Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000; **321:**199–204.
29 Morrow DA, Ridker PM. C-reactive protein, inflammation and coronary risk. *Med Clin N Am* 2000; **84:**149–61.
30 Lucas AD, Greaves DR. Atherosclerosis: Role of chemokines and macrophages. *Exp Rev Mol Med* 2001; 1–18. www-ermm.cbcu.cam.ac.uk/01003696h.htm
31 Yla-Herttuala S, Lifton B, Rosenfeld M *et al.* Expression of MCP-I in macrophage-rich areas of human and rabbit atherosclerotic lesions. *Proc Nat Acad Sci USA* 1991; **88:**5252–56.
32 Nelken N, Coughlin S, Gordon D, Wilcox J. MCP-I in human atheromatous plaques. *J Clin Invest* 1991; **88:**1121–7.
33 Stemme S, Holm J, Hansson GK. T lymphocytes in human atherosclerotic plaques are memory cells expressing CD45RO and the integrin VLA-1. *Arterioscler Thromb* 1992; **12:**206–11.
34 Hansson GK, Hellstrand M, Rymo L, Rubbia L, Gabbiani G. Interferon-γ inhibits both proliferation and expression of differentiation-specific α-smooth muscle actin in arterial smooth muscle cells. *J Exp Med* 1989; **170:**1595–1608.
35 Amento EP, Ehsani N, Palmer H, Libby P. Cytokines and growth factors positively and negatively regulate interstitial collagen gene expression in human vascular smooth muscle cells. *Arteriosler Thromb* 1991; **11:**1223–30.
36 Liuzzo G, Biasucci LM, Gallimore JR *et al.* The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994; **331:**417–24.
37 Haverkate F, Thompson SG, Pyke SDM, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. *Lancet* 1997; **349:**462–6.
38 Danesh J, Whincup P, Walker M *et al.* Low grade inflammation and coronary heart disease: prospective study and meta-analysis. *BMJ* 2000; **321:**208–13.
39 Danesh J, Muir J, Wong YK, Ward M, Gallimore JR, Pepys MB. Risk factors for coronary heart disease and acute-phase proteins: a population based study. *Eur Heart J* 1999; **20:**954–9.
40 Danesh J, Wheeler JG, Hirshfield GM *et al.* C reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *New Eng J Med* 2004; **350:**1387–97.
41 Scandinavian Simvastatin Survival Study Group, Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344:**1383–1389.
42 Shepherd J, Cobbe S M, Ford I *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. *N Engl J Med* 1995; **333:**1301–1307.
43 Sacks FM, Pfeffer MA, Moye LA *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; **335:**1001–1009.
44 Heart Protection Study collaboration group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360(9326):**7–22.
45 Shepherd J. Lipids in health and disease. *Biochem Soc Trans* 2004; **32(Pt 6):**1051.
46 Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. *Lancet* 1997; **348:**1079–82.
47 Padgett RC, Heistad DD, Mugge A, Armstrong ML, Piegors DJ, Lopez JAG. Vascular responses to activated leukocytes after regression of atherosclerosis. *Circ Res* 1992; **70:**423–9.
48 Small DM. George Lyman Duff memorial lecture. Progression and regression of atherosclerotic lesions. Insights from lipid physical biochemistry. *Arteriosclerosis* 1988; **8:**103–29.
49 Loree HM, Tobias BJ, Gibson LJ, Kamm RD, Small DM, Lee RT. Mechanical properties of model atherosclerotic lesion lipid pools. *Arterioscler Thromb* 1994; **14:**230–4.
50 Ehrenstein MR, Jury EC, Mauri C. Statins for atherosclerosis – As good as it gets? *N Eng J Med* 2005; **352(1):**73–5.
51 Cutts JL, Bankhurst AD. Suppression of lymphoid cell function in vitro by inhibition of HMG CoA reductase by lovastatin. *Int J Immunopharmac* 1989; **11:**863–869.
52 Cutts JL, Scallen TJ, Watson J, Bankhurst AD. The role of mevalonic acid in the regulation of natural killer cell cytotoxicity. *J Cell Physiol* 1989; **139:**550–7.
53 Kobashigawa J, Katznelson S, Laks H *et al.* Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 1995; **333:**621–627.
54 Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105:**1135–43.
55 Rosensen R, Tangney CC, Casey LC. Inhbition of proinflammatory cytokine production by pravastatin. *Lancet* 1999; **353:**983–4.
56 Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The CARE Investigators. *Circulation* 1999; **100:**230–5.
57 Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation* 2001; **103:**1933–5.
58 Albert MA, Staggers J, Chew P, Ridker PM. The pravastatin inflammation CRO evaluation (PRINCE): rationale and design. *Am Heart J* 2001; **141:**893–8.
59 Ridker PM, Cannon CP, Morrow D, Rifai N *et al.* C-reactive protein levels and outcomes after statin therapy. *N Eng J Med* 352; **1:**20–8.
60 Davignon J, Mabile L. Mechanisms of action of statins and their pleiotropic effects. *Ann Endocrinol* 2001; **62:**101–112.
61 Martin G *et al.* Statin-induced inhibition of the Rho-signaling pathway activates PPARalpha and induces HDL apoA-I. *J Clin Invest* 2001; **107:**1423–32.
62 Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; **286:**64–70.
63 Ortego M, Bustos C, Hernandez-Presa MA, Tunon J, Diaz C, Hernandez G, Egido J. Atorvastatin reduces NF-kappaB activation and chemokine expression in vascular smooth muscle cells and mononuclear cells. *Atherosclerosis* 1999; **147:**253–61.
64 Pahan K, Sheikh FG, Namboodiri AM, Singh I. Lovastatin and phneylacetate inhibit the induction of nitric oxide synthase and cytokines in rat primary astrocytes, microglia, and macrophages. *J Clin Invest* 1997; **100:**2671–9.
65 Kothe H, Dalhoff K, Rupp J *et al.* Hydroxymethylglutaryl conezyme A reductase inhibitiors modify the inflammatory response of human macrophages and endothelial cells infected with Chlamydia pneumoniae. *Circulation* 2000; **101:**1760–3.
66 Inoue I, Goto S, Mizotani K *et al.* Lipophilic HMG-CoA reductase inhibitor has an anti-inflammatory effect: reduction of mRNA levels for interleukin-1β, interleukin-6, cyclooxygenase-2, and p22phox by regulation of peroxisome proliferator-activated receptor-α (PPAR-α) in primary endothelial cells. *Life Sci* 2000; **67:**863–876.
67 Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med* 2000; **6:**1399–1402.
68 Weitz-Schmidt G *et al.* Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nat Med* 2001; **7:**687–92.
69 McCarty MF. Reduction of serum C-reactive protein by statin therapy may reflect decreased isoprenylation of Rac-1, a mediator of the IL-6 signal transduction pathway. *Med Hypotheses* 2003; **60(5):**634–9.
70 Nissen SE, Murat Tuzcu E, Schoenhagen P, Crowe T *et al.* Statin therapy, LDL cholesterol, C-reactive protein and coronary artery disease. *N Eng J Med* 2005; **352(1):**29–38.
71 McCarey DW, McInnes IB, Madhok R, Hampson R *et al.* Trial of atorvastatin in rheumatoid arthritis (TARA): double-blind, randomised, placebo-controlled trial. *Lancet* 2004; **363:**2015–21.
72 Stevens R, Douglas K, Saratzis A, Kitas GD. Inflammation and atherosclerosis in rheumatoid arthritis. *Exp Rev Molec Med* 2005; **7:**1–24.