Viewpoint

Put your heart into the joint benefits of statins!

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The recognition that systemic inflammatory diseases are associated with accelerated atherosclerosis offers the prospect of reducing morbidity and mortality of affected patients by attention to traditional cardiovascular risk factors. For example, in most studies of mortality in patients with rheumatoid arthritis, excess cardiovascular deaths predominate, with a risk ratio of about 2 (reviewed by Van Doornum [1]). Several recent observations indicate that not only is chronic inflammation associated with atherosclerosis but aberrant cellular and humoral immune responses are integral to its pathogenesis (reviewed by Sherer and Shoenfeld [2]). It has become apparent that therapeutic interventions in chronic inflammatory and cardiovascular disease might be closely intertwined. Also emerging is the realisation that agents prescribed as either immunomodulators or lipid modulators might be acting in both capacities. Statins are particularly topical in this regard.

Statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) are widely prescribed for individuals at increased risk from cardiovascular disease (reviewed by Singh and Mehta [3]). HMG-CoA reductase is an enzyme of the cholesterol biosynthetic pathway that catalyses the conversion of HMG-CoA to mevalonic acid. Downstream metabolites in this pathway include farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are required for post-translational prenylation of a range of moieties, including signalling intermediaries, tRNA and coenzyme Q in the electron transport chain (reviewed in Holstein et al. [4]). It follows that, in addition to decreasing cholesterol levels, statins can be expected to have diverse effects on cell physiology.

In 1995 it was reported that pravastatin decreased the incidence of haemodynamically significant rejection episodes in cardiac transplant patients and that this effect was independent of the decrease in cholesterol levels [5]. Subsequent studies have revealed a wide range of statin-sensitive immunological pathways. For example, statins bind to β_2 integrin and thereby block T-cell costimulation by means of lymphocyte-function-associated antigen-1 (LFA-1) [6]. Statins inhibit interferon-γ-inducible class II transactivator (CIITA) to decrease the induction/upregulation of MHC class II molecules on professional and non-professional antigen-presenting cells [7]. In monocytes and/or macrophages, statins decrease chemotaxis, lipopolysaccharide (LPS)-mediated release of tumour necrosis factor-α (TNF-α) activation of NO synthase [8] and LPS-stimulated secretion of matrix metalloproteinase-9 [9]. These immunological effects indicate that statins might interfere with the initiation and amplification of immune/inflammatory responses. The appeal of statin therapy in chronic inflammatory disease is further enhanced by accumulating evidence that statins might influence bone metabolism (reviewed by Bauer [10]).

Although the observation that statins prevented rejection episodes after cardiac transplant suggests that significant immunomodulatory effects can be obtained *in vivo*, some subsequent clinical data have been equivocal and most investigations have demonstrated effects on pathways *in vitro*. Oral atorvastatin was recently shown to prevent or reverse either chronic or relapsing paralysis in a murine model of demyelination [11]. This was associated with a shift from T helper (Th)1-type immune responses towards Th2-type responses *in vivo*.

Could statins have such impressive effects in a model of inflammatory arthritis? Leung and colleagues chose the well-characterised model of collagen-induced arthritis in the arthritis-susceptible DBA/1j mouse strain, in which arthritis is induced 25–35 days after immunisation with bovine type II collagen emulsifed in complete Freund's adjuvant [12]. Simvastatin was administered daily at 10, 20 or 40 mg/kg. These doses are higher than those used in

HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; IFN = interferon; i.p. = intraperitoneally; LPS = lipopolysaccharide; Th = T helper cell; TNF = tumour necrosis factor.

humans because of the relatively rapid induction of HMG-CoA reductase in rodents [13] and, apparently, even the administration of 40 mg/kg simvastatin was not associated with a significant decrease in plasma cholesterol concentration in mice. Both 'prophylactic' and 'therapeutic' simvastatin regimes were investigated. Prophylactic daily administration of simvastatin intraperitoneally (i.p.) was begun 21 days after the initial immunisation with type II collagen/adjuvant; that is, several days before the onset of arthritis. The therapeutic regime consisted of 40 mg/kg daily simvastatin i.p. for 14 days, starting on the day after the onset of arthritis (8–14 mice per group).

Simvastatin at a dose of 40 mg/kg per day significantly decreased the severity of arthritis in both the prophylactic and therapeutic groups. This dose also decreased the incidence of arthritis by about 50% in the prophylactic group. Lower doses of simvastatin had no significant effect on these outcomes. Treatment with 40 mg/kg simvastatin decreased serum interleukin-6 levels as well as synovial cellular infiltration and joint destruction. There was also evidence for a decrease in Th1-type responses, although in contrast with previous studies there was no clear increase of Th2-type activity. The effect of incubation with simvastatin on human cells *in vitro* was studied with peripheral blood mononuclear cells from patients with rheumatoid arthritis and normal controls, and with synovial fluid mononuclear cells from patients with rheumatoid arthritis. Simvastatin decreased proliferation and IFN-γ production with no apparent decrease in T cell viability in each of the study groups (statins have effects in promoting apoptosis). Co-culture experiments indicated that statins decrease the T cell-stimulated secretion of TNF-α by macrophages.

Patients with chronic inflammatory disease should be treated aggressively to decrease cardiovascular risk as well as to control disease activity. The evidence that statins are immunomodulatory and that they mitigate demyelination and inflammatory arthritis in rodent models is compelling. Can such effects be achieved in human disease? Studies in patients with chronic inflammation are needed to assess whether statins have significant effects on disease activity and tissue damage, as well as cardiovascular disease and, perhaps, also bone mineral density and risk of fracture. Carefully designed and adequately powered studies will be required to address these issues and to investigate the interaction of statins with a range of traditional and biological disease-modifying agents.

Because statins inhibit the production of mevalonate, they interfere with the biosynthetic pathways of both sterols and isoprenoids. Inhibition of the prenylation of proteins and lipids might have both deleterious and beneficial effects on cell physiology. For example, it has been suggested that a lack of CoA prenylation might interfere with the function of this component of the electron transport chain. This deficit, in a tissue dependent on oxidative metabolism, might contribute to the occurrence of statin-associated myositis [14]. Dissection of the relative importance of blockade of sterol and isoprene pathways for each of the statin-mediated effects might lead to a range of novel anti-inflammatory and anti-proliferative agents or to a new generation of lipid modulators, with improved side-effect profiles. Patients with chronic inflammatory disease have accelerated atherosclerosis and are at increased risk for myocardial infarction, congestive cardiac failure and stroke. Many of these patients are also at risk for osteoporosis. The effects of statins on lipid profiles, immunological pathways and bone metabolism might offer a single agent to contribute to three important therapeutic objectives in chronic inflammatory disease. It is more likely that specifically designed derivatives of statins with enhanced immunomodulatory and tissue modulatory effects will emerge.

Competing interests

None declared.

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Note

* These papers have been highlighted by Faculty of 1000, a web-based literature awareness service. F1000 evaluations for these papers are available on our website at http://arthritis-research.com/viewpoints/reflinks5_04.asp

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