Statins in rheumatology.

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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Over the past 40 years, there has been a revolution in understanding atherosclerosis. The process of atherosclerosis is not simply the bland accumulation of lipids within the artery wall. The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses, which are best described as a chronic inflammatory disease. According to the “response to injury” model of atherosclerosis, the first step is injury to the endothelial cells lining the arterial wall. How that injury occurs is, at present, unknown but is key to the prevention of atherosclerosis.

Fully half of all patients with atherosclerotic coronary artery disease do not have any of the established risk factors (hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, marked obesity, and physical inactivity). This had led to the concept of inflammation as a cardiovascular risk factor. The inflammatory processes in atherosclerosis resemble those in rheumatoid arthritis (RA). Monocyte activation, T and B cell activation, endothelial cell activation, and elevation of C-reactive proteins (CRP) are seen in both. The inflammatory processes inherent in RA may promote atherosclerosis.

Since the 1950s, it has been appreciated that RA patients die earlier. The mean standardized mortality rate on pooled analysis in RA is 1.70. That excess mortality is mostly due to cardiovascular disease. The high incidence of cardiovascular events in RA appears to be independent of the traditional cardiovascular risk factors. That premature atherosclerosis may be a consequence of the chronic inflammation that is part and parcel of RA. Bacon and colleagues speculate that endothelial dysfunction related to rheumatoid vasculitis is a strong candidate for the initiating factor in the accelerated cardiovascular mortality of RA. Chronic endothelial cell dysfunction may leave the vessels in RA with an enhanced susceptibility to both classic cardiovascular risk factors and RA related ones, which may interact in complex ways. Reduction of the inflammatory process by disease modifying antirheumatic drugs (DMARD) such as methotrexate may reduce the excess cardiovascular mortality.

Pincus and Callahan wrote an editorial in The Journal in 1986 on the excess mortality in RA. Ironically, in retrospect, they noted that the survival rate for RA with severe functional impairment was comparable to those individuals with triple vessel coronary artery disease. The survival rates may have been comparable because a goodly number of those rheumatoid patients also had coronary artery disease.

Although effective treatment of RA may reduce the risk of atherosclerosis, one would not expect that the treatment of atherosclerosis would improve the clinical features of RA. Curiously enough, there is some evidence to support that possibility. Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] are potent inhibitors of cholesterol biosynthesis. Statins bind to HMG-CoA reductase, leading to competitive displacement of the natural substrate, HMG-CoA. Inhibition of cholesterol biosynthesis is accompanied by an increase in hepatic low density lipoprotein (LDL) receptors, which promote uptake and clearance of cholesterol from the blood. Structural differences among the statins result in variable lipophilicity, half-life, and potency.

In vitro, over the past 15 years, it has been discovered that statins affect more than just cholesterol levels. Statins influence several other cellular pathways including those involving inflammatory, oxidative, angiogenic, and thrombotic processes. Most of those effects are thought to be mediated through isoprenoids. Statins, through their inhibition of the mevalonate pathway, can reduce isoprenoid levels. Isoprenoids are important intermediates in the mevalonate pathway. They are small lipid moieties that attach to several GTP binding proteins including Ras and Rho. This lipid attachment, termed isoprenylation, permits anchoring of the protein in the cell membrane. Members of the Ras super-family then act as molecular switches, transducing a wide array of extracellular growth and differentiation signals from the cell surface receptors to the nucleus. Pathways affected include cell proliferation, cell differentiation, vesicular transport, and apoptosis.

See Association of statin use and development and progression of hip OA in elderly women, page 106.
The statin-induced decrease in isoprenylation of signaling molecules such as Ras and Rho leads to modulation of various signaling pathways including those involving bone morphogenic protein-2, endothelial nitric oxide synthase, tissue-type plasminogen activator, endothelin-1, and plasminogen activator inhibitor-1. The expression of inducible MHC class II is inhibited. CD40 expression in vascular endothelial cells is decreased. Antiinflammatory and immunomodulatory effects can be reversed completely or in part with the administration of mevalonate\textsuperscript{14}.

In vitro, there is also evidence that statins have important immunomodulatory and antiinflammatory effects independent of the mevalonate pathway. Statins selectively inhibit leukocyte function antigen-1 mediated adhesion and costimulation of lymphocytes, with resulting suppression of the inflammatory response\textsuperscript{15}.

There are interesting although limited data on the effect of statins in animal models of rheumatic disease. Certain antiphospholipid antibodies (aPL), particularly those directed against B\textsubscript{2}-glycoprotein I, bind to vascular endothelial cells and induce a procoagulant phenotype including the increased expression of adhesion molecules. Ferrera, et al showed that fluvastatin significantly diminishes aPL-mediated thrombosis and endothelial activation \textit{in vivo} in CD-1 male mice receiving purified IgG from patients with the antiphospholipid syndrome\textsuperscript{16}. Leung and colleagues looked at the effect of simvastatin on collagen-induced arthritis\textsuperscript{17}. Arthritis in this TH-1-driven mouse model develops a month or so after immunization with collagen, that is, 4 to 14 days before the onset of arthritis. In the therapy group, the drug was given one day after the onset of arthritis.

When given as prophylaxis, simvastatin reduced the incidence of arthritis by 50% and significantly reduced the mean articular index. When given as treatment one day after onset of arthritis, simvastatin significantly reduced the mean articular index as well as the mean number of arthritic paws. Those good effects in the therapy and the prophylaxis groups were seen only with simvastatin given in high dose (40 mg/kg/day).

Mice were treated with saline or high dose simvastatin (40 mg/kg) starting one day after onset of their arthritis. After 14 days of simvastatin treatment, the arthritic paws were removed and stained with H and E or toluidine blue. Profound cartilage surface erosion and loss of proteoglycan were seen in the control group. The histological appearances were scored for the presence of synovial bone erosion, hyperplasia, and cellular infiltration. All those scores were significantly less in the simvastatin treatment group. In \textit{vitro} there was significant suppression of the collagen-specific TH-1 humoral and cellular immune response in the high dose simvastatin treated mice.

With such obvious antiinflammatory and immunomodulating effects \textit{in vitro} and in animal models, one might expect similar effects in human rheumatic disease. Those studies, limited in number, show only a modest effect. One hundred sixteen patients with RA were randomized in a double-blind placebo-controlled trial to receive 40 mg of atorvastatin or placebo as an adjunct to existing DMARD therapy\textsuperscript{18}. A marked suppression of acute phase reactants (CRP and erythrocyte sedimentation rate declined by 50% and 28%, respectively) but only a modest effect on disease activity (Disease Activity Score-28 improvement of 0.5) was seen after 6 months of treatment. A significant improvement in the lipid profile in individuals receiving atorvastatin was also seen.

In this issue of \textit{The Journal}, Beattie, et al utilized the population database of the Study of Osteoporotic Fractures to examine the association of radiographic hip osteoarthritis (OA) with statin use\textsuperscript{19}. Of interest was their observation of the very modest but significant increase in the risk of radiographic findings of hip OA in those women exposed to statins. Also noted was a nonsignificant trend indicating that statins were not associated with worsening of structural disease.

The quite modest effect of statins in the management of human rheumatic disease may relate to the dose or to the differences between mouse, man, and test tube. More prospective trials of statins in the various rheumatic diseases are needed to determine if the effects are clinically significant. Certainly the concentrations used to demonstrate the biologic effects of statins in cell culture and animal experiments, especially with regard to inhibition of rho geranylgeranylation would need to be considered more carefully.
tion, are much higher than those prescribed clinically. However, the development of novel agents based on a better understanding of the in vitro effects of statins may result in a new generation of drugs effective for rheumatic conditions.

Clearly, statins are indicated in the management of hypercholesterolemia in patients with RA just as in normal individuals. Despite current DMARD treatment, many of our rheumatoid patients still have significant systemic inflammatory disease. Whether such patients with normal or even low cholesterol levels require treatment with statins in order to prevent adverse cardiovascular events is unknown. The potential role of statins in the prevention of cardiovascular events in individuals with evidence of systemic inflammation will be addressed in the JUPITER trial. That trial will enroll 15,000 individuals with average LDL cholesterol (< 3.36 mmol/l) and elevated levels of high sensitivity CRP (> 2.0 mg/l) to investigate the effect of rosuvastatin in the primary prevention of major cardiovascular events. Unfortunately, individuals with chronic inflammatory diseases such as RA or lupus are excluded from this study. Because JUPITER is evaluating an agent that dramatically lowers LDL cholesterol as well as high sensitivity (hs) CRP, it will not directly answer whether hsCRP reduction alone leads to reduced vascular risk. That hypothesis will require trials of agents with anti-inflammatory effects without cholesterol lowering actions. Hopefully we can collaborate with our cardiology colleagues in such future studies.

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REFERENCES