

Pleiotropic effects of statins in inflammation: friend or foe in human arthritis?

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The statins (competitive HMG-CoA reductase inhibitors) form a class of hypolipidemic drugs used to lower cholesterol and triglycerides and are beneficial in primary and secondary prevention of coronary diseases. Recent studies indicate that statins, while curtailing cholesterol synthesis, exhibit alternate and/or pleiotropic effects attenuating inflammation, oxidative stress, endothelial function and thrombogenic responses. McCarey *et al.* show beneficial effects of statins on C-reactive protein, erythrocyte sedimentation and joint swelling in rheumatoid arthritis (RA), illustrating a role for statins in inflammation resolution. This paper brings to light several alternate effects of statins, specifically those associated with inflammation resolution and immune modulation, in addition to cardiovascular risks. Although 'killing two birds with one stone' is quite appealing, as described by McCarey *et al.*, there are caveats in applying this approach too broadly. Clinical efficacy, long-term safety effects and the possibility of unwanted immune modulation warrant contemplation. Moreover, a particular statin may be contraindicated in some types of arthritis, whereas unwanted side effects on a molecular level or null clinical outcomes may result.

Rheumatoid arthritis (RA), a chronic disease causing pain, stiffness and swelling of the joints, is an autoimmune and inflammatory disorder affecting approximately 1% of the global population. RA is characterized by inflammatory synovitis, cartilage destruction, peripheral inflammation and accelerated atherogenesis. Symptoms of RA develop between the ages of 35 and 50 years, with women being affected 2–3-times more often than men. Cardiovascular disease (CVD) is recognized as a leading cause of death in RA patients, resulting in a 40% mortality rate [1]. There are twofold increases in risk for myocardial infarction and stroke in RA patients; this risk increases to threefold in patients suffering disease for 10 years or more. Although the increased CVD risk factors in RA patients seem to be independent of arthritis, they may also overlap with traditional risk factors, as decreases in endothelial function, endothelial progenitor cells and arterial stiffness are all common in RA patients with accelerated atherosclerosis. Reduction of the CVD burden in RA patients is a complex process when compared with non-RA patients, due to inadequate inflammation suppression, as well as the need for multiple, concomitant drug therapies [2]. This clustering of CVD risk factors and other cardiovascular risks in RA make the statins promising candidates to manage the symptoms and progression of RA. The clinical application of statins is evolving due to their pleiotropic actions [3,4], and curtailing inflammation and CVD risks with statins in RA is tempting [2].

Clinical outcomes in RA

Early studies by McCarey *et al.* [5] demonstrated the beneficial effects of atorvastatin in RA within 6 months of initiation of treatment. A significant improvement of the Disease Activity Score (DAS 28 EULAR) was observed in patients with RA when compared with placebo [5]. An improved DAS 28 EULAR response was observed in 31% of atorvastatin-treated patients. A significant decrease was seen in the both the levels of C-reactive protein and the erythrocyte sedimentation ratio, by approximately 50 and 28%, respectively. Although a decrease in swollen joint count and IL-6 was noted, adverse events occurred with similar frequency in both the atorvastatin and placebo groups. As expected, many of the cardiovascular risk factors declined in the atorvastatin-treated individuals as compared with placebo groups. Similar observations resulted from a prospective study of 7512 patients by Okamoto *et al.* [6], suggesting statins in general ameliorate RA and are useful in RA therapy. Moreover, in additional studies with atorvastatin, a significant reduction in arterial stiffness in RA was observed [7].

Pleiotropic effects

Statins exhibit other biological effects: stimulation of bone formation, alteration of function of endothelial cells, induction of apoptosis, inhibition of tumor growth, inhibition of integrin expression, disruption of T-cell activation and reduction of inflammation [3,4,8–10]. These collateral effects result from the inhibition of HMG-CoA reductase. There is a consensus among investigators that

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some of these may be due to modulation of prenylation and/or geranylgeranylation of critical signaling molecules such as Rho, GTPase and others [4,11–13]. The Th1-driven model of murine inflammatory arthritis showed reduced proliferation of mononuclear cells and suppression of cytokines by simvastatin [14]. Similar treatment of mice with an apolipoprotein A-1 mimetic peptide, in combination with pravastatin, inhibited collagen-induced arthritis (CIA) [15]. Funk *et al.* [16] demonstrated that simvastatin protects periarticular bone in RA joints via suppression of inflammation-induced bone resorption. Similar studies by Palmer *et al.* [17] using a CIA murine model treated with atorvastatin and rosuvastatin showed no clinical efficacy. In contrast, although simvastatin treatment resulted in beneficial effects, increased glucocorticoids were seen as an undesirable side effect. Thus, demonstrating a differential effect of statins *in vivo*. It should be noted that in some of these animal experiments, statins were used at least tenfold higher concentrations as compared with the recommended concentrations in humans.

An understanding of statin mechanisms at the cellular level may help to explain some of these benefits in RA patients, including, but not limited to:

- Inhibition of IL-1, IL-6 and IL-8 production
- Inhibition of TNF α -induced proliferation of synovial cells
- Synovial cell apoptosis
- Reduction of TH1:TH2 and CD4:CD8 ratios [18–21]

Additionally, simvastatin also augments neutrophil apoptosis [10]. The modulation of endothelial CD56 and decay-accelerating factor (DAF) receptors by atorvastatin under hypoxic conditions may inhibit early and late complement activation [22]. The pleiotropic effects of statins were observed when fluvastatin, but not pravastatin, induced apoptosis in fibroblast-like synoviocytes from patients with RA [11]. Gene-expression studies from our laboratory compared the application of therapeutic concentrations of two distinct (structurally and metabolically) statins on human osteoblast cells stimulated with IL-1 for 24 h, defining inflammation resolution/pleiotropic signatures of these statins. The effects of lovastatin or simvastatin on mRNA expression during the inflammatory response was broad, considering that over 600 transcripts were modulated by these statins. Furthermore, these compounds not only showed a common signature for the two statins (as seen in

light blue in Figure 1) but demonstrated ‘private signatures’, representing each distinct statin type (as shown in green and purple in Figure 1). These preliminary experiments indicate the complexity and versatility of statin compounds on inflamed osteoblast cells.

Statins, inflammation & other arthritic conditions

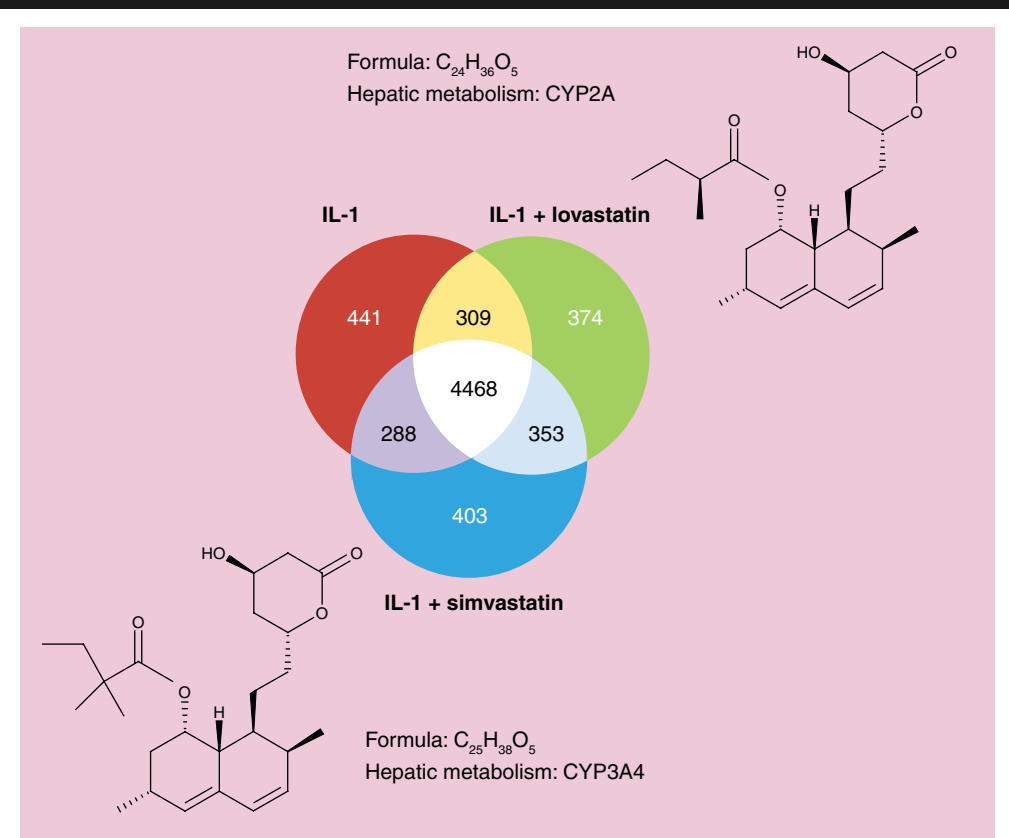
Classical and/or ovate inflammation has been observed in osteoporosis, osteoarthritis (OA) and lupus erythematosus (SLE). The effects of statins in osteoporosis, OA and SLE are not encouraging. Although certain statins are capable of modulating bone mass and/or bone resorption in rodents [23,24], simvastatin did not prevent, nor restore, ovariectomy-induced bone loss in adult mice [25]. Human studies in postmenopausal women demonstrated that statins did not improve fracture risk or bone density [26]. Therefore, human evidence does not warrant the use of statins to prevent or treat osteoporosis. Additional studies have shown that statins may minutely increase the risk of developing hip OA; however, statins do not worsen progression of existing hip OA [27]. Simvastatin has been reported to decrease proteinuria in SLE [4]. Increased cases of statin-induced lupus-like syndrome have recently been reported [28], with most cases linked to the use of second-generation statins. Statin-induced lupus showed skin eruptions and antinuclear antibodies similar to SLE [4,29].

In summary, the studies described in this paper demonstrate the efficacy of using atorvastatin to prevent cardiovascular risks in RA, along with additional beneficial effects in inflammation resolution. The statin-sensitive biochemical pathway offers further targets for the generation of new, disease-modifying drugs to treat chronic inflammatory diseases [8,30–32]. The multiple secondary targets of statins and distinct hepatic metabolism within this class of drugs, coupled with the complexity of arthritis as a disease, suggests that statins act as ‘a double-edged sword’ in treatment of some types of arthritic diseases. Therefore, adhering to clinical practice guidelines, which are based on published evidence and expert opinion, is essential [32].

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Figure 1. Gene expression of mRNA transcripts in activated human osteoblast cells in the presence of statins.



Human osteoblast cells were grown *in vitro*. They were stimulated with IL-1 for 24 h in the presence of two different statins at therapeutic concentrations. The figure shows the structure and physical properties of lovastatin and simvastatin. Total RNA was extracted and assayed for gene expression using an Affymetrix gene chip. The bioinformatic analysis and resulting Venn diagram were generated using GeneSpring software. After normalizing the data, the genes were filtered based on expression: twofold change for upregulated transcripts and a 0.5-fold for downregulated transcripts as previously reported [34,35]. The data show differential and common modulation of transcripts by two different statins. Similar observations were made when using primary human endothelial cells in similar experiments.

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Executive summary

- McCarey and colleagues describe the use of statins in rheumatoid arthritis (RA).
- The 'inflammation resolution' activity of statins is distinct and complex, as demonstrated by the differing efficacies of functionally common (HMG-CoA inhibitors), but structurally distinct, statins in various types of arthritic diseases.
- Although the distinct mechanism of action of statins in RA proves elusive, significant enthusiasm for clinical application to restrict cardiovascular disease risk and inflammation in treatment of RA has been established.
- Long-term controlled studies with larger cohorts and other classes of statins are essential to further evaluate the efficacy of this line of treatment in RA.

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