

Statins as Anti-inflammatory Therapy in HIV Disease?

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(See the article by Ganesan et al., on pages 756–764.)

Statins are lipid-lowering, anti-inflammatory, and potentially antiretroviral drugs. Statins inhibit hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, which is a precursor of sterols, including cholesterol. Hepatic triglycerides and cholesterol are incorporated into very low-density lipoprotein (VLDL) and released into the circulation for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Statins lower plasma total and LDL cholesterol levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL. Multiple studies have found that statins safely prevent atherosclerotic disease, which has resulted in the widespread use of statin therapy.

Only part of the reduced incidence of cardiovascular disease with statin therapy can be explained by its lipid-lowering effect [1]. Some of the residual benefit is associated with reduction in plasma levels of the pro-inflammatory protein, C-reactive protein, which is a reduction that appears to occur independently of the effect of statin therapy on lipid levels [2–5], the mechanism of which is unknown.

Statins also have cellular immunological effects that might relate to cardiovascular disease prevention: inhibition of T cell proliferation and interferon γ expression through a HMG-CoA-dependent pathway that involves inhibition of T cell KLF2 gene expression; inhibition of MHC class II expression; inhibition of C-reactive protein-induced chemokine secretion, ICAM-1 upregulation and chemotaxis in adherent human monocytes; increased recruitment of regulatory T cells; induction of apoptosis of human T and B lymphocytes; and decreased CD40 expression on and CD40-related activation of vascular endothelial cells [6–11].

Statins have also been found in some, but not all, studies to inhibit human immunodeficiency virus (HIV) replication in vitro [12–15]. The mechanism of this effect is unclear. The only randomized trial to address this issue, however, found that atorvastatin therapy begun at the time of interruption of antiretroviral therapy did not affect the

rate or magnitude of rebound HIV viremia [16].

In the study reported by Ganesan et al [17] in this issue of *The Journal*, HIV-infected adults not receiving antiretroviral therapy and with levels of LDL cholesterol lower than what would require therapy were randomized to receive high-dose atorvastatin or placebo for 8 weeks. Atorvastatin had no effect on plasma HIV RNA load despite good adherence to therapy and a >30% decrease in plasma LDL cholesterol levels. Analysis of secondary end points, however, found statistically significant reductions in some markers (HLA-DR and CD38) of immune activation on both CD4+ and CD8+ T lymphocytes of 2.5%–5.0%, changes similar to those previously observed with lower-dose atorvastatin (but not simvastatin) over a 14-day period in healthy adults [18], but which did not correlate with changes in LDL cholesterol levels.

Levels of T lymphocyte activation are associated with more rapid progression of HIV disease in untreated adults [19–21]. The magnitude of change in these levels that is associated with clinically relevant differences in the rates of HIV disease progression is unknown. So, although they are statistically significant, it is not clear whether the decreases in T lymphocyte activation observed among those subjects who received atorvastatin are clinically significant.

Potential conflicts of interest: none reported.

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The Journal of Infectious Diseases 2011;203:751–752

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1537-6613/2011/2036-0001\$15.00

DOI: 10.1093/infdis/jiq120

The present study has additional limitations. Unfortunately, levels of inflammatory serum proteins, such as C-reactive protein, were not measured. Moreover, the duration of statin exposure was only 8 weeks, so it is not known whether the anti-inflammatory effects observed would be sustained with longer statin exposure.

Unless other statins have modes of action that are different from those of high-dose atorvastatin, it seems unlikely that other statins will be found to suppress HIV replication. However, the present data suggest that statins merit evaluation over longer periods in HIV-infected adults who are receiving effective antiretroviral therapy but who have persistent T cell activation, given that ongoing inflammation in HIV-infected adults receiving therapy is associated with a greater risk of HIV disease progression and death. A very large study would probably be required to determine whether the potentially positive effects of statin therapy on inflammatory biomarkers will translate into less HIV disease progression and fewer cases of inflammatory non-AIDS-related illnesses, such as cardiovascular disease and end-stage liver disease.

Funding

A.C. has received research funding from GlaxoSmithKline/ViiV Healthcare and Merck; consultancy fees from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare and Merck; lecture sponsorships from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare and Merck; and has served on advisory boards for Abbott, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, Merck and Roche.

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