What Are Pleiotropic Effects? The Role of Statins in Decreasing Inflammation

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Statin pleiotropy is an important concept. Because decreases in cholesterol levels account for no more than 30% of the advantageous effects of statins on cardiovascular risk, myriad other positive actions contingent on statins will help define and (we hope) ameliorate residual risk.

The pleiotropic effects attributed to statins are many.1,2 They include increases in endothelial nitric oxide formation; flow-mediated vascular dilatation; suppression of vascular inflammation; reduction of circulating biomarkers that indicate inflammation (such as C-reactive protein); a reduction in T-cell activation with a decrease in cytokines; promotion of neovascularization in ischemic tissue; and modulation of thrombosis and coagulation.

A review of some of the trials that evaluated the pleiotropic effects of statins will inform further understanding.

In the REVERSAL Trial3 and Substudy4 (Reversal of Atherosclerosis with Aggressive Lipid Lowering), 654 patients with known coronary artery disease received either atorvastatin, 80 mg/d, or pravastatin, 40 mg/d. The primary end-point was a decrease in atheroma volume as measured by intravascular ultrasound (IVUS). After 18 months, not only was cholesterol lowering greater in the atorvastatin limb (see below), but C-reactive protein was also decreased more in the atorvastatin limb (36% lower than baseline with atorvastatin versus only 5% with pravastatin). The primary end point—atheroma progression—was compared in the two groups. Disease had not progressed in the atorvastatin-treated individuals, but it did in those taking pravastatin.

The next study in the REVERSAL series is critical to the inflammation-cardiovascular risk theory. In the substudy of REVERSE,4 LDL levels in the atorvastatin and pravastatin groups during therapy were 76.7 and 110.8 mg/dL, respectively. Using a similar follow-up technique, IVUS, vascular benefit (characterized as “constrictive wall remodeling”) was significantly correlated with reductions in C-reactive protein level from baseline through statin therapy, but not with changes from baseline in LDL-C or HDL-C values during statin therapy. Even though cholesterol lowering was of a greater magnitude in the atorvastatin recipients, the significant correlate with improvement was the drop in the inflammatory marker. The authors’ conclusion was that “Plaque-stabilizing therapy with statin medications . . . appears to be related to their anti-inflammatory effects.”

Lest one believe that REVERSAL is the only series to assess anti-inflammatory effects contingent to statins, a number of other, disparate “inflammatory” lesions have benefitted. These include renal function after acute coronary syndromes and heart catheterization5; outcomes after other percutaneous vascular procedures6; and remodeling/intimal hyperplasia after venous bypass grafts.7 This list is abbreviated significantly!

The best way to bring statin anti-inflammatory actions and cardiovascular disease back into focus
would be to address risk reduction in disorders characterized by inflammation. HIV/AIDS is a good place to begin. Read my column on HIV/AIDS, Cardiovascular Disease, and Inflammation for more on that topic.

References


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