Effect of Hydroxymethyl Glutaryl Coenzyme A Reductase Inhibitor Therapy on High Sensitive C-Reactive Protein Levels

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Background—Prospective studies indicate that baseline levels of C-reactive protein (CRP), the prototypic marker of inflammation, are associated with an increased risk for cardiovascular events. Limited studies have examined therapies that influence high-sensitive CRP (hs-CRP) levels, especially in hyperlipidemic patients. Thus, we tested the effects of 3 hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins), simvastatin (20 mg/d), pravastatin (40 mg/d), and atorvastatin (10 mg/d), on levels of hs-CRP in a randomized, double-blind, crossover trial of 22 patients with combined hyperlipidemia (LDL cholesterol $>130$ mg/dL and triglycerides of 200 to 600 mg/dL).

Methods and Results—After 6 weeks of an American Heart Association Step 1 diet, fasting blood samples were drawn at baseline and after 6 weeks of therapy with each drug. hs-CRP levels were significantly decreased after treatment with all 3 statins compared with baseline (median values: baseline, 2.6 mg/L; atorvastatin, 1.7 mg/L; simvastatin, 1.7 mg/L; and pravastatin, 1.9 mg/L; $P<0.025$). The reductions obtained with the 3 statins were similar. In addition, there was no significant effect on either plasma interleukin-6 or interleukin-6 soluble receptor levels. There was no relationship between reductions in hs-CRP and LDL cholesterol.

Conclusions—Pravastatin, simvastatin, and atorvastatin significantly decreased levels of hs-CRP. These data support an anti-inflammatory effect of these drugs. (Circulation. 2001;103:1933-1935.)

Key Words: statins | inflammation | C-reactive protein

Recently, numerous trials with the hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) demonstrated a significant reduction in cardiovascular events. Although the majority of the effect could be ascribed to a beneficial effect on the lipid profile, the statins might have additional effects that could confer benefit. Inflammation seems to be a pivotal final step in acute coronary syndromes. The advent of a highly sensitive assay for C-reactive protein (CRP) has led to a greater understanding of the role of inflammation in coronary artery disease. CRP, a prototypic marker of inflammation, is driven by the proinflammatory cytokines interleukin (IL)-1, tumor necrosis factor-$\alpha$, and IL-6. Numerous prospective epidemiological studies have clearly demonstrated an increased risk with increasing CRP levels. In addition, studies have demonstrated that CRP confers risk above that of an abnormal lipid profile. Thus, modalities targeting inflammation and reducing proinflammatory cytokines and CRP levels could be a potential additional strategy in the prevention of cardiovascular disease.

Regarding the statins, one study to date demonstrated that patients who have increased CRP levels (increased inflammation) have a greater benefit from pravastatin therapy and that median CRP levels were reduced 17.4% in the group that received pravastatin. Thus, it is important to determine whether this reduction in CRP is specific for pravastatin or if it also occurs with other commonly prescribed statins. The aim of the present study was to test if simvastatin and atorvastatin, at LDL-lowering doses similar to those of pravastatin (as determined by the CURVES study), resulted in a significant reduction in high-sensitive CRP levels (hs-CRP).

Methods

Patients

Patients were recruited from the Lipid Clinics at the University of Texas Southwestern Medical Center in Dallas. This protocol was approved by the Institutional Review Board, and all patients gave informed consent. Inclusion criteria for the subjects included an age of 18 to 70 years, a triglyceride level between 200 to 600 mg/dL, and an LDL cholesterol level $\geq 130$ mg/dL.
Exclusion criteria were as follows: use of lipid-lowering drugs or drugs known to affect lipid metabolism, use of antioxidant supplements, use of warfarin or heparin for the past 4 weeks, liver or renal dysfunction, diabetes, hypothyroidism, infection, cancer, and/or recent major surgery or illness.

**Study Design**

This was a randomized, double-blind, crossover study design. A total of 22 patients were enrolled. There was a 6-week lead-in dietary phase when the patients were instructed by the dietitian to follow an American Heart Association Step 1 diet for the study duration, followed by a 6-week drug therapy phase with a 3-week washout period between drugs. The statins used included simvastatin (20 mg/d), atorvastatin (10 mg/d), and pravastatin (40 mg/d).

Three fasting blood samples were obtained at baseline (7 days apart), and 2 fasting blood samples were obtained during therapy with each drug (5.5 and 6 weeks). Levels of total cholesterol, total triglycerides, and LDL and HDL cholesterol were assayed by routine laboratory techniques, as reported previously. Levels of CRP were measured by a highly sensitive nephelometric assay using a monoclonal antibody to CRP coated on polystyrene beads (Dade Behring). This assay is referenced to the World Health Organization standard and is sensitive in the range of 0.175 to 60 mg/L. Both interassay and intra-assay coefficients of variation were 5%. IL-6 and IL-6 soluble receptor levels in serum were measured using a highly sensitive immunoassay (R&D Systems). The intra-assay coefficient of variation was <4%.

**Statistical Analyses**

All statistical analyses were performed using SAS version 8.0. Because some variables were skewed (triglycerides, hs-CRP), non-parametric tests were used for these data. The number of replicates needed to achieve the validity coefficient of cholesterol (0.91) with CRP was 2. Treatment order for this crossover study was assessed with repeated measures ANOVA models using log transformations for skewed data.

The 3 statin drugs were compared with Friedman’s test and Wilcoxon signed rank test for pairwise comparisons: the means of the 3 baseline levels were compared with the 2 levels obtained on therapy. Weighted correlation coefficients were computed to assess associations between variables of interest. The level of significance was set at P<0.05 (2-sided).

**Results**

The salient characteristics of the participants in this study are as follows: age, 47.2±9.7 years; male/female ratio, 10/12; and body mass index, 24.5±4.9 kg/m². As is evident in the Table, there was a significant reduction in total and LDL cholesterol with all 3 statins; a significant reduction in plasma triglycerides was only seen with simvastatin and atorvastatin. None of the drugs had a significant effect on HDL cholesterol with all 3 statins; a significant reduction in plasma triglycerides was only seen with simvastatin and atorvastatin.

There were no significant differences in the median percent reduction in hs-CRP levels with pravastatin, simvastatin, and atorvastatin (20.3%, 22.8%, and 28.3%, respectively). Of the responders, ≥40% of the reduction in CRP was seen in 31.3%, 38.8%, and 44.4% of patients receiving pravastatin, simvastatin, and atorvastatin, respectively.

Neither plasma IL-6 nor IL-6 soluble receptor levels were significantly reduced with any of the drugs (IL-6: baseline, 2.5±0.4 pg/mL; pravastatin, 2.6±0.5 pg/mL; simvastatin, 2.4±0.4 pg/mL; and atorvastatin, 2.8±0.5 pg/mL; IL-6 soluble receptor: baseline, 21.5±8.1 ng/mL; pravastatin, 21.0±7.5 ng/mL; simvastatin, 21.3±9.0 ng/mL; atorvastatin, 21.7±8.4 ng/mL; P=0.4). Although no significant correlation was found between changes in CRP levels and changes in LDL cholesterol (r=−0.1, P=0.7) or HDL cholesterol (r=0.04, P=0.9), the correlation with triglycerides was significant (r=0.59, P=0.005). Furthermore, while in the washout phase, LDL-cholesterol increased significantly (P<0.001) but, compared with the drug phase, there was no significant increase in CRP levels (P=0.21).

**Discussion**

Whether CRP is a risk marker or risk factor will only be settled by future studies. To date, CRP has been localized to foam cells in atherosclerotic lesions, it colocalizes with activated complement fragments, and it induces adhesion
molecule expression from the endothelium and tissue factor secretion from monocytes.\textsuperscript{3,12,13} Previously, Ridker et al\textsuperscript{18} showed that patients with hs-CRP levels in the upper quartile had a greater benefit (54\% relative risk reduction) compared with those in the lowest quartile. Furthermore, they showed a significant reduction in hs-CRP with pravastatin therapy. In the present report, we confirm that pravastatin therapy results in a significant reduction in CRP levels. Furthermore, we show that simvastatin and atorvastatin also result in a significant reduction in CRP levels. There was no significant difference between the 3 statins regarding reductions in hs-CRP. Like the Cholesterol And Recurrent Events (CARE) study, we showed no significant correlations between total cholesterol, LDL cholesterol, or HDL cholesterol and hs-CRP levels. The increase in LDL-cholesterol but not CRP in the washout phase further underscores a divergence of statins on these 2 effects. However, we found a significant correlation between a reduction in triglycerides and hs-CRP levels. Because our sample size is small and pravastatin reduced CRP without having a significant effect on triglycerides, these findings need to be viewed with caution, and confirmation must await future studies.

This study explored a potential mechanism by which statins may result in a significant reduction in hs-CRP levels. IL-6 levels were measured, but statin drugs had no effect on IL-6 levels. Because there is a great circadian variation in IL-6 levels and our sample size is small, this finding needs to be viewed with caution. Plasma IL-6 may not be the best reflection of the IL-6 levels that bathe the liver. More meaningful data would have been obtained if IL-6 levels were measured after activation, because statin therapy resulted in a significant reduction in IL-6 in lipopolysaccharide-activated whole blood.\textsuperscript{14} Because IL-6 soluble receptor levels did not change, a decrease in IL-6 soluble receptor levels cannot explain the reduction in CRP.\textsuperscript{15} Another potential reason for a failure to see a reduction in IL-6 levels despite a reduction in CRP could be that statins are acting through IL-6-independent mechanisms.\textsuperscript{16}

In conclusion, the present study makes the novel observation that pravastatin, atorvastatin, and simvastatin therapy result in a significant reduction in hs-CRP levels. Furthermore, all 3 statins reduced hs-CRP levels to a similar extent.

Recently, the present investigators showed that high-dose RRR-\textalpha tocopherol (1200 IU/d) resulted in a reduction in plasma hs-CRP levels and monocyte IL-6 levels in both controls and type 2 diabetic patients.\textsuperscript{17} In the Physician’s Health Study, patients with the highest CRP levels received the greatest benefit from aspirin therapy.\textsuperscript{18} Although studies with aspirin therapy are conflicting,\textsuperscript{19,20} the benefit of statins in reducing hs-CRP levels is supported by at least 2 studies to date. Further studies need to be directed toward elucidating the mechanism of reduction in CRP.

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