Editorial

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Anti-Inflammatory Effects of Statins Beyond Cholesterol Lowering

Seung-Jae Joo, MD

Cardiology Division, Department of Internal Medicine, Jeju National University Hospital, Jeju, Korea

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Statins lower low density lipoprotein-cholesterol (LDL-C) level by inhibiting 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase. A meta-analysis of the primary and secondary prevention trials of statin therapy demonstrated the reduction of major coronary events, coronary revascularization, and stroke by 20% per 1 mmol/L (39 mg/dL) reduction in LDL-C levels,[1] and a linear relationship was shown between the cardiovascular event (coronary death or non-fatal myocardial infarction) rates and LDL-C level, during statin therapy in secondary prevention studies.[2]

It has been known for many years that atherosclerosis may be an inflammatory disease. The evolution of the atherosclerotic plaque is closely related to the inflammatory processes, such as the recruitment of inflammatory monocytes into the vascular wall, the transformation of monocytes into macrophages and foam cells, the release of multiple cytokines and growth factors attracting vascular smooth muscle cells, weakening of a fibrous cap by matrix metalloproteinase and the rupture of plaques with thrombus formation.[3] Among the markers of systemic inflammation, C-reactive protein (CRP), which are synthesized by liver under the control of inflammatory cytokines including interleukin (IL)-6, has been shown to best predict future cardiovascular events. In a large, long-term prospective study, the odds ratio for coronary heart disease was 1.45 in people of the top third of CRP values after the adjustment of established risk factors.[4] However, because the elevated CRP concentration are associated with all the conventional risk factors of coronary artery disease, there have been debates whether inflammation is an independent risk factor or just only a marker of the conventional risk factors. One meta-analysis of 54 long-term prospective studies, including 1.6 million people without a history of vascular diseases, demonstrated a log-linear association of CRP concentration with the coronary heart disease and vascular mortality. This association was persisted, but weakened after the adjustment for several traditional risk factors.[5]

Numerous laboratory and clinical studies suggested the LDL-independent or "pleiotropic" effects of statins, such as anti-inflammatory effect, immunomodulation, increase in circulating endothelial progenitor cells, up-regulation of endothelial nitric oxide synthesis, and modulation of thrombosis and coagulation.[6] Statins interfere with the mevalonate pathway by inhibiting HMG-CoA reductase, which involves the synthesis of isoprenoids, such as geranylgeranyl pyrophosphate (GGPP). Prenylation of Rho proteins by GGPP induces a down-regulation on endothelial nitric oxide synthase (eNOS) expression. Statins inhibit Rho prenylation, resulting in increased eNOS expression. Anti-inflammatory effects of statins are thought to be related to the inhibition of Ras prenylation.[6]

Lowering of CRP level after statin therapy in clinical trials is cited as one of the evidences that support the anti-inflammatory effect of statins, irrespective of lipid lowering. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering trial, the progression of atherosclerosis in patients with angiographically documented coronary disease was examined by intravascular ultrasound after a moderate or intensive statin treatment.[7] After 18 months, the mean LDL-C level was reduced from 150.2 to 94.5 mg/dL and the mean CRP level decreased from 2.9 to 2.3 mg/L. Although there was a weak, but significant correlation between the reduction in LDL-C levels and that in CRP levels, the decrease in CRP levels was independently and significantly correlated with the rate of progression after the adjust-

Correspondence: Seung-Jae Joo, MD, Cardiology Division, Department of Internal Medicine, Jeju National University Hospital, 15 Aran 13-gil, Jeju 690-767, Korea
Tel: 82-64-717-1701, Fax: 82-64-757-8276
E-mail: sejjoo@jejunu.ac.kr

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ment for the reduction in LDL-C, apolipoprotein B-100, and non-high density lipoprotein cholesterol levels. Patients with reductions in both LDL-C and CRP that were greater than the median had significantly slower rates of progression.

However, a different point of view exists that the pleiotropic effect of statins may not contribute to an additional benefit of cardiovascular risk reduction beyond LDL-C lowering effect. In one meta-regression analysis, data from 5 diet, 3 bile acid sequestrant, 1 surgery, and 10 statin trials were analyzed.[8] They found that the non-statin interventions, as well as statins, seemed to reduce the coronary heart disease risk in a similar pattern, consistent with a one-to-one relationship between LDL-C lowering and the reduction of coronary heart disease. These results suggested that anti-inflammatory effects of statins rather be the result of the reduction of LDL-C. A strong correlation between the change in LDL-C and CRP was also exhibited in a meta-analysis, including 23 randomized placebo-controlled trials treated with a variety of statins, nonstatin drugs, or other regimens.[9] Statin therapies had no significant effect on CRP level after the adjustment for the change in LDL-C, supporting that LDL-C lowering itself other than pleiotropic effects may be the main cause of anti-inflammatory effects of statins. In a meta-analysis of cardiovascular outcome trials comparing the intensive versus moderate statin therapy in patients with coronary artery diseases, standard-dose therapy lowered LDL-C by 22% to the mean of 101 mg/dL, whereas, high-dose therapy reduced it by 42% to the mean of 75 mg/dL.[10] This 25.7% difference in LDL-C level between the 2 treatment groups was associated with a 16% odds reduction in coronary death or myocardial infarction, and a 16% odds reduction in coronary death or any cardiovascular events, supporting a "lower LDL-C is better" strategy.

Recent clinical trials have more advocated the LDL-C-independent, anti-inflammatory effects of statins. The Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin study is the randomized placebo-controlled trial, which evaluated the effect of rosuvastatin on 2-year change in carotid intima media thickness in low-risk patients with elevated LDL-C. Rosuvastatin treatment was associated with a 36% reduction in CRP level and a 49% reduction in LDL-C level, but there was no relationship between the change in CRP and the change in LDL-C.[11] The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study was a randomized, double-blind, placebo-controlled primary prevention trial of rosuvastatin in 17802 apparently healthy people without hyperlipidemia (LDL-C <130 mg/dL), but with elevated high-sensitivity (hs)-CRP (≥2 mg/L).[12] Rosuvastatin reduced LDL-C levels by 50% and hs-CRP levels by 37%. These effects translated into 54% reduction of myocardial infarction, 48% reduction of stroke, 47% reduction of revascularization or unstable angina, and 20% reduction of death from any cause. These effects were consistent in all the subgroups evaluated, including people with LDL-C levels of ≤100 mg/dL, and those with elevated levels of hs-CRP, but no other major risk factors. Increasing the baseline hs-CRP levels were associated with increasing the vascular risk, and the absolute risk reduction was the greatest among those with the highest hs-CRP levels.[13]

In this issue of the journal, Kim et al.[14] have reported the effect of doubling the statin dose on pro-inflammatory cytokine and CRP levels in patients with triple-vessel coronary artery disease documented by the coronary angiogrphy. Because all enrolled patients were already taking statins, their initial LDL-C level was low (83±20 mg/dL), but CRP level was still high (3.4±4.1 mg/L). After 3 months, CRP level declined to 1.2±1.4 mg/L (p=0.004) and IL-6 declined from 8.55±3.98 to 4.81±2.58 pg/dL (p<0.001), but serum lipid levels did not change. Double statin dose decreased LDL-C level by 6% (from 83±20 to 77±20 mg/dL), but statistically insignificant. Because of a small sample size and a short-term follow-up period of 3 months, neither the coronary risk reduction nor change of angina symptom could be demonstrated. This study has several limitations. First, they used 3 different kinds of statin with different doses. Second, the initial mean CRP level was high, but the range of CRP was wide. Third, clinical outcomes could not be evaluated in this small group of patients with only 3-month treatment. All these problems may be solved in a larger group of patients with a longer term follow-up and the subgroup analysis of heterogeneous variables. Despite these limitations, this study provided the additional evidence of LDL-C-independent, anti-inflammatory effects of statins in patients with stable angina and low LDL-C level.

C-reactive protein levels after statin therapy influenced the clinical outcomes. Relationships between the LDL-C and CRP levels achieved after intensive versus moderate statin therapy and the risk of recurrent myocardial infarction or death from coronary causes were evaluated in patients with acute coronary syndromes.[15] This study showed better clinical outcomes in patients with low CRP levels after statin therapy, regardless of the resultant level of LDL-C. Even in patients with post-treatment LDL-C levels <70 mg/dL, the rates of recurrent events were lower among those with CRP levels <2 mg/L. In JUPITER trial, a 65% reduction in vascular events in participants who achieved both LDL-C <70 mg/dL and hs-CRP <2 mg/L, versus a 33% reduction in those who achieved one or neither target compared with the controls were shown.[16] A CRP target, as well as a LDL target, may be considered in statin therapy.

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