Original Article

http://dx.doi.org/10.4070/kcj.2012.42.9.595
Print ISSN 1738-5520 • On-line ISSN 1738-5555

kcj
Korean Circulation Journal

The Effect of Doubling the Statin Dose on Pro-Inflammatory Cytokine in Patients With Triple-Vessel Coronary Artery Disease

Yoo Ri Kim, MD[1], Jae Hong Park, MD[2], Hye-Jin Lee, MD[3], Wouk Bum Pyun, MD[4], and Si-Hoon Park, MD[4]

[1]*Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul,*
[2]*Department of Cardiology, Han-Il General Hospital, Seoul,*
[3]*Departments of Endocrinology and* [4]*Cardiology, Ewah Womans University School of Medicine, Ewha University Medical Center, Seoul, Korea*

Background and Objectives: Statin prevents atherosclerotic progression and helps to stabilize the plaque. According to a recent study, statin reduces inflammation in blood vessels. However, it has not been demonstrated to have any anti-inflammation reaction in patients who have been diagnosed as having a triple-vessel coronary artery disease (CAD).

Subjects and Methods: This study included a total of thirty (30) patients who had been diagnosed by coronary angiogram as having a triple-vessel CAD. Patients who already had been taking statin were given doubled dosage. An interview, physical examination and blood test were performed at the beginning of this study and three months later.

Results: After doubling the dose of statin, there was no statistically significant decrease in total cholesterol, low density lipoprotein-cholesterol, (increase in) high density lipoprotein-cholesterol and triglyceride in the blood test. C-reactive protein (CRP), an acute phase reactant, significantly decreased from 0.34 mg/dL at the beginning of the study to 0.12 mg/dL at the end of study ($p<0.01$). The interleukin-6 concentration also significantly decreased from 8.55 pg/dL to 4.81 pg/dL ($p<0.001$). No major cardiovascular events occurred and the dosage regimen was not modified during the close observation period. There was no difference in the symptoms of angina pectoris, established by World Health Organization Angina Questionnaires, before and after the dose increase. Liver enzymes remained within normal range with no significant increase before and after conducting this study.

Conclusion: Doubling the dose of statin alone significantly lowers pro-inflammatory cytokine concentration, which is closely related to the potential acute coronary syndrome, and CRP, a marker of vascular inflammation. **(Korean Circ J 2012;42:595-599)**

KEY WORDS: Statin; C-reactive protein; Interleukin-6.

Introduction

Growing evidence supports the role of statins in local and systemic inflammation with respect to common pathophysiology in the atherosclerotic progression of the plaque.[1)]

Circulating inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are moderately associated with a risk of coronary heart disease events.[2)] These inflammatory biomarkers independently predict further vascular events in healthy people without hyperlipidemia. A recently published study an association between CRP and stable coronary disease regardless of low density lipoprotein-cholesterol (LDL-C) levels.[3)] However, the therapeutic dose and duration of statin as an anti-inflammatory have been little studied. Previous evidence regarding the effect of statins across differing regimens on future cardiac events in high risk patients with advanced coronary disease are inadequate. The objective of this study was to document changes of the inflammatory biomarkers after doubling the dose of statin in high risk patients who had been diagnosed by coronary angiography as having a triple-vessel coronary artery disease (CAD).

Received: November 3, 2011
Revision Received: February 1, 2012
Accepted: March 15, 2012
Correspondence: Si-Hoon Park, MD, Department of Cardiology, Ewha Womans University School of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 158-710, Korea
Tel: 82-2-2650-5019, Fax: 82-2-2655-2076
E-mail: sihoon@ewha.ac.kr

• The authors have no financial conflicts of interest.

Subjects and Methods

Study design

This study included thirty (30) patients who were recruited from Ewha Womans University Mokdong Hospital from May 2008 to January 2009 and had been diagnosed by coronary angiography as having a triple-vessel CAD at least a year prior to the enrollment. Patients with these coronary arterial lesions were either not treatable by current angioplasty techniques or refused to undergo coronary artery interventions. All patients were already taking a statin.

The exclusion criteria included myocardial infarction, unstable angina, stroke and any other vascular episodes within six months, and lack of previous statin use. Thirty patients were followed up for three months after doubling the dose of statin. Nineteen patients had been taking atorvastatin 10 mg and the dose was increased to 20 mg. One patient had been taking atorvastatin 20 mg and the dose was increased to 40 mg. Five patients had been taking pravastatin 40 mg and the dose was increased to 80 mg. The others have been taking pitavastatin 2 mg and the dose was increased to 4 mg.

At each visit, blood pressure, heart rate, weight and height were measured while their concurrent medications in addition to statin were verified. The primary end point was the concentration change of CRP or IL-6. The secondary end points were major cardiac adverse events such as death, myocardial infarction, stroke, any revascularization and typical anginal symptoms, as assessed by the WHO Angina Questionnaire.[4)5)]

Laboratory aspects

Lipid serum levels, CRP, IL-6, creatinine and liver enzymes were measured. The creatinine clearance was calculated from serum creatinine values by using the Modification of Diet in Renal Disease equation.[6)] IL-6 was assayed on the saved ultra-low temperature freezer in 2009, using a high sensitivity Enzyme-linked immunosorbent assay (R&D systems, Minneapolis, MN, USA). Sampling was performed with a sensitivity of less than 0.16 pg/mL before and after doubling the dose of statin.

C-reactive protein levels were measured immediately after sampling by using an automated particle-enhanced turbid metric immunoassay (Hitachi, Tokyo, Japan) with a sensitivity of <0.03 mg/dL. All samples were processed by technicians who were not informed of the clinical data.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 16.0 software (SPSS, Chicago, IL, USA) was used for data analysis.

Continuous variables were expressed as the mean±standard deviations while categorical variables were stated as numbers and proportions (%). This single group investigation involved tests taken before and after change in dosage regimen. In order to demonstrate the effect of statin therapy on inflammatory biomarkers, paired sample t-tests were applied to continuous variables of the lipid profiles, inflammatory markers, body mass index and the levels of liver enzymes. A p of less than 0.05 was considered statistically significant.

Results

Demographic and other information of patients in this study are summarized in Table 1. The mean age was sixty-five years old and 60% of these patients were males. Cardiovascular disease risk factors in these patients are smoking (63%), hypertension (23%) and diabetes mellitus (40%). The changes of serum lipid levels are shown in Table 2. The mean total cholesterol, LDL-C, high density lipoprotein-cholesterol and triglyceride did not change significantly after doubling the dose of statin.

The safety and clinical profiles are shown in Table 3. There were no major adverse cardiac events and only two patients had chest discomfort during this study. The patients who had replied positively to the WHO Angina Questionnaires before the study, did not change their answers when they were asked again at the end of the study. The mean alanine aminotransferase level was in the normal range before and after doubling the dose of statin.

Mean body mass index was changed from 23.3 kg/m^2 to 23.2 kg/m^2, and was not statistically significant. The average CRP concentration decreased from 0.34 mg/dL at the beginning to 0.12 mg/dL at the end of the study after three months (p<0.01). The mean IL-6

Table 1. Characteristics of patients before doubling statin dose

Characteristics (n=30)	
Age (years)	65±9 (45-86)
Gender, male (%)	18 (60.0)
Body mass index (kg/m^2)	23.3±2.6
Estimated GFR (mL/s per 1.73 m^2)*	73.6±18.0
Risk factors, no. of patients (%)	
Smoking	19 (63.3)
Hypertension	23 (76.7)
Diabetes mellitus	12 (40.0)
Duration of statin treatment (days)	796±511 (367-2240)
Doses of statins	
Atorvastatin 10 mg	19 (63.3)
Atorvastatin 20 mg	1 (3.3)
Pravastain 40 mg	5 (16.7)
Pitavastain 2 mg	5 (16.7)

*Calculated from the serum creatinine value by using the Modification of Diet in Renal Disease equation.[6)] GFR: glomerular filtration rate

level decreased from 8.55 pg/dL at the beginning of the study to 4.81 pg/dL at the end of the study (p<0.001).

Doubling the dose of statin was associated with a 63% reduction in CRP and 43% reduction in IL-6 in three (3) months (p<0.01) (Fig. 1).

Table 2. Changes of lipid and biomarker level before and after doubling dose of statin

Lipid (mg/dL)	Doubling dose of statin				
	Before	After			
	Mean	Mean	ΔChange	p	95% CI
Total cholesterol	156±39	149 ±32	-7	0.270	-6.01-21.08
LDL-C	83±20	77±20	-6	0.110	-1.64-14.71
HDL-C	42±10	45±14	+2	0.070	-6.15-0.22
Triglycerides	134±60	124±68	-10	0.280	-9.24-30.98
CRP (mg/dL)	0.34±0.41	0.12±0.14	-0.2	0.004	0.07-0.35
IL-6 (pg/dL)	8.55±3.98	4.81±2.58	-3.7	<0.001	1.97-5.51

HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, CI: confidence interval, CRP: C-reactive protein, IL-6: interleukin-6

Table 3. Safety and clinical profiles before and after doubling dose of statin

Properties	Before doubling dose of statin (n=30)	After doubling dose of statin (n=30)	p
Mean, ALT (IU/L)	19±4	20±7	0.91
MACE			
Death		0	
MI		0	
Stroke		0	
Any revascularization		0	
Positive angina questionnaire (%)†	2 (3.3)	2 (3.3)*	1.00
Body mass index (kg/m²)	23.3±2.6	23.2±2.6	0.26

*Same patients before doubling dose of statin, †Quantification of the WHO Angina Questionnaire.[4)5)] ALT: alanine aminotrasferase, MACE: major adverse cardiac event, MI: myocardial infarction

Concurrent medications prescribed, along with statins, were anti platelet agents, nitrates, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin-receptor II blockers, calcium channel blockers and diuretics in a decreasing order. Regular medications were continued with statin administration for the duration of this study.

The proportion of patients receiving anti-angina medications such as nitrates and beta blockers was similar in both groups at the beginning and at the end of this study. However, in most cases, the nitrate prescribed was only nitroglycerin to be taken as needed.

Discussion

The role of inflammation in the pathogenesis of atherosclerotic coronary disease has been extensively investigated over the last twenty years.[7)] The balance of pro-inflammatory and anti-inflammatory agents may determine the vascular health or illness.

The most extensively studied and controversial topic has been the high-sensitivity CRP, an acute phase reactant.[8)9)] Multiple studies, including several meta-analyses, have demonstrated CRP to be an independent predictor of cardiovascular risks.[10)] Among numerous circulating inflammatory biomarkers, IL-6 has been found to be a moderate indicator for 1) acute coronary syndrome and 2) augmented risk for cardiovascular diseases like Type-2 diabetes mellitus.[8)] IL-6 has a pleiotropic effect and affects systemic inflammations through its actions on hematopoiesis and many cell types of the immune system. IL-6 is perhaps one of the major factors that induce acute phase reactants such as CRP from the liver. IL-6 is implicated in the activation of the endothelium and promotes the development of functional and structural vascular changes. It contributes to atherogenesis and plaque vulnerability.[11)]

A significant decrease in CRP or IL-6 in patients treated with an increased statin dosage regimen was evident in this study. Patients with a triple-vessel CAD are at high risk of future adverse vascular

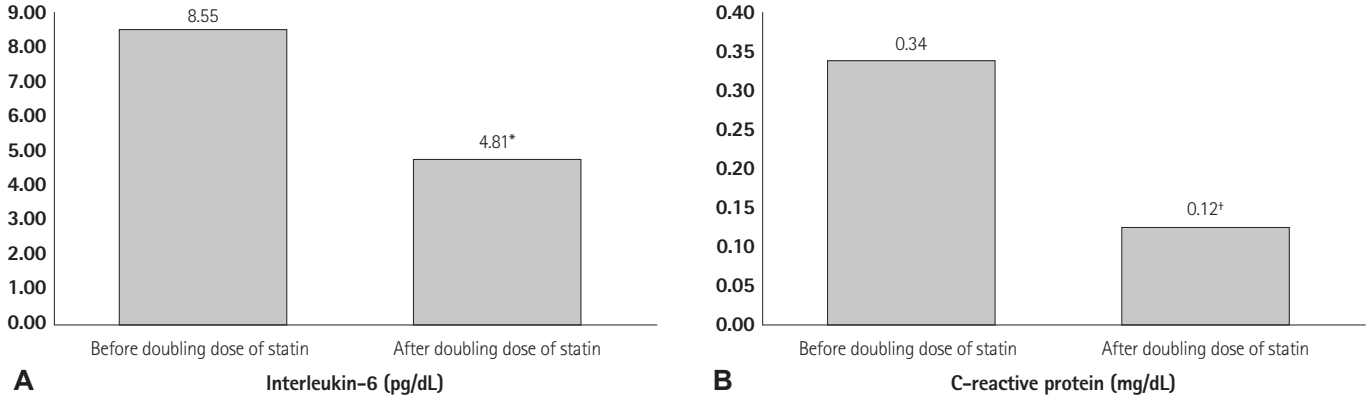

Fig. 1. Changes of C-reactive protein (A) and Interleukin-6 (B) concentrations before and after doubling the statin dose. *p<0.001, †p<0.01 denotes that the reduction was significantly different before and after doubling the dose of statin therapy.

http://dx.doi.org/10.4070/kcj.2012.42.9.595

events. To the best of our knowledge, no other study to date has examined pro-inflammatory cytokine IL-6 and acute phase reactant CRP, evaluating systemic inflammation in this setting. We found that doubling the doses of statin significantly decreased the concentrations of CRP and IL-6, but without significant lipid level change.

Statins have been recognized for having anti-inflammatory and antioxidant properties. Other studies suggested that these so-called 'pleiotropic' effects might account for some of the benefits of statins beyond the aspect of lowering the LDL-C level.[12)13)]

The Measurement of CRP for the targeting of statin therapy in the primary prevention of acute coronary events trial demonstrated a reduction in CRP {74%; 95% confidence interval (CI) 71-75, p<0.001}, independent of initial LDL-C level in a high-dose atorvastatin group.[14)] In the pre-specified analysis of the A to Z trial of a recent report, the lower levels of achieved CRP in 30 days and in 4 months were found to be independently associated with improved long-term survival.

Indeed, patients with CRP levels greater than 0.3 mg/dL had more than a three-fold higher risk of death {hazard ratio (HR) 3.7; 95% CI 1.9-7.2}. However, patients with CRP levels of 0.1-0.3 mg/dL had a greater than a two-fold higher risk of death (HR 2.3; 95% CI 1.2-4.6) when compared with patients with CRP <0.1 mg/dL.[15)]

The sub-analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trial demonstrated that patients who achieved lower CRP levels regardless of achieved LDL-C levels had better clinical outcomes than those with elevated CRP.[16)]

Consequently, our data showed that simply doubling the dose of statin not only significantly reduced the CRP concentrations, but also dramatically decreased the concentrations of IL-6, a pro-inflammatory cytokine. Recent investigations have indicated that various biomarkers, such as inflammatory cytokines, cellular adhesion molecules and acute phase reactants are closely related to plaque destabilization and rupture.[17)] These biomarkers might provide an earlier indication of overall patient risks and aid in identifying patients with a higher risk of having adverse events.[9)] Statins promote the potent systemic anti-oxidant effect through suppression of the distinct oxidation pathways.[13)]

This study could help clarify the role of statin in systemic vascular inflammation and atherosclerosis, but several limitations should be noted. First, patients subjected to this study were composed largely of older patients over 60 years old and the results might not be pertinent to other age groups.

Second, this study had a relatively small number of patients who satisfied tight inclusion and exclusion criteria and did not have a control group that maintained the baseline initial dose of statin. Thus, taking measurements of CRP and IL-6 in a group with a single dosage regimen would most likely be biased. As well, it explains that the change of LDL-C was 6% which is consistent with the well known effect of statin dose doubling but statistically insignificant in this study.

Third, this study had short-term follow-ups of only three months. Major adverse cardiovascular events did not occur in these patients. It might be due to insufficient time to observe adverse events .

With respect to safety, the risk of statin-associated increased liver enzymes and in turn liver damage or rhabdomyolysis may not be related to the extent of LDL-C lowering. However, the risk of cancer might be significantly associated with lower achieved LDL-C levels.[18)] In our study, neither rhabdomyolysis nor elevated liver enzymes were noted. Owing to short study duration, the long-term effects of the treatment could not be proven relative to cancer risks. A large clinical study showed that additional clinical benefits could be achieved by more aggressively treating older patients with a coronary heart disease in an effort to reduce LDL-C levels at less than 100 mg/dL. Furthermore, their findings supported the use of intensive LDL-C lowering therapy in high-risk older patients with an established cardiovascular disease.[19)]

Until the results of additional long-term trials in a larger number of patients become available, aggressive lipid lowering with a high-dose statin regimen appears to be as safe and effective as the standard care in triple-vessel CAD which could not be treated by angioplasty.

In conclusion, doubling of the statin dose alone significantly lowers the pro-inflammatory cytokine concentration, which is closely related to the potential acute coronary syndrome, and CRP, a marker of vascular inflammation in patients with established coronary heart disease without adverse events. Previous data show that inflammatory processes are involved in all stages of atherosclerosis in various medical settings while increased pro-inflammatory factors result in rupture of atherosclerotic plaques.

The concentrations of CRP and IL-6 decreased regardless of lipid levels. These findings should carefully be applied to patients with a triple-vessel CAD, in whom percutaneous coronary intervention could not be performed.

References

1. Libby P, Sasiela W. Plaque stabilization: can we turn theory into evidence? *Am J Cardiol* 2006;98(11A):26P-33P.
2. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350:1387-97.
3. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-207.
4. Biloglav Z, Ivanković D, Campbell H, Rudan I. Performance of WHO Angina Questionnaire in measuring burden of coronary heart disease in human isolate populations. *Coll Antropol* 2004;28:205-13.

5. Murphy NF, Stewart S, Hart CL, MacIntyre K, Hole D, McMurray JJ. A population study of the long-term consequences of Rose angina: 20-year follow-up of the Renfrew-Paisley Study. *Heart* 2006;92:1739-46.
6. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation: modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-70.
7. Mills R, Bhatt DL. The Yin and Yang of arterial inflammation. *J Am Coll Cardiol* 2004;44:50-2.
8. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001;286:327-34.
9. Apple FS, Wu AH, Mair J, et al. Future biomarkers for detection of ischemia and risk stratification in acute coronary syndrome. *Clin Chem* 2005;51:810-24.
10. Shishehbor MH, Bhatt DL, Topol EJ. Using C-reactive protein to assess cardiovascular disease risk. *Cleve Clin J Med* 2003;70:634-40.
11. Kofler S, Nickel T, Weis M. Role of cytokines in cardiovascular diseases: a focus on endothelial responses to inflammation. *Clin Sci (Lond)* 2005;108:205-13.
12. LaRosa JC. Pleiotropic effects of statins and their clinical significance. *Am J Cardiol* 2001;88:291-3.
13. Shishehbor MH, Brennan ML, Aviles RJ, et al. Statins promote potent systemic antioxidant effects through specific inflammatory pathways. *Circulation* 2003;108:426-31.
14. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344:1959-65.
15. Morrow DA, de Lemos JA, Sabatine MS, et al. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation* 2006;114:281-8.
16. Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l: an analysis of the PROVE-IT TIMI-22 Trial. *J Am Coll Cardiol* 2005;45:1644-8.
17. Ambrose JA, Martinez EE. A new paradigm for plaque stabilization. *Circulation* 2002;105:2000-4.
18. Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials. *J Am Coll Cardiol* 2007;50:409-18.
19. Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK; the Treating to New Targets Study Steering Committee and Investigators. Outcomes of using high- or low- dose atorvastatin in patients 65 years age or older with stable coronary heart disease. *Ann Intern Med* 2007;147:1-9.

http://dx.doi.org/10.4070/kcj.2012.42.9.595