The Short-term Effect of Atorvastatin on Flow-Mediated Vasodilation, Pulse Wave Velocity and Carotid Intima-Media Thickness in Patients With Moderate Cholesterolemia

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ABSTRACT

Background and Objectives: The mechanism for the improved endothelial function after treatment with statins has been shown to be the increased bioavailability of nitric oxide, which is independent of the cholesterol-lowering effects of statin therapy. The aim of this study was to evaluate the short-term effect on flow-mediated vasodilation (FMD), the pulse wave velocity (PWV) and the carotid intima-media thickness (IMT) of statin treatment, as based on the dose and duration of therapy.

Subjects and Methods: We enrolled 51 patients with moderate cholesterolemia (total cholesterol: 200-250 mg/dL). The patients were randomly divided into two groups according to the dose of atorvastatin (10 mg: 27 patients, 40 mg: 24 patients). We measured the FMD of the brachial artery, the carotid-radial PWV, the IMT of both common carotid arteries, the lipid profile and the serum C-reactive protein (CRP) at baseline, one week and eight weeks after statin treatment.

Results: The total cholesterol and low density lipoprotein (LDL) cholesterol levels in both groups were significantly decreased one week and eight weeks later. However, a difference between the groups was only noted at eight weeks. The FMD for both groups was significantly increased at one and eight weeks; however, the difference was not significantly different between the two groups. The carotid-radial PWV of the 40 mg group was decreased at one and eight weeks, and the change of the PWV at eight weeks was significantly different between the two groups. However, the change in the PWV was not correlated with a change in the LDL-cholesterol. Conclusion: Early improvement of the FMD and PWV following statin treatment might be related to the dose and duration of statin therapy and these effects of statin treatment may be independent of lipid lowering. (Korean Circ J 2008;38:144-151)

KEY WORDS: Atherosclerosis; Hydroxymethylglutaryl coenzyme A reductase inhibitors.

Introduction

The endothelium is the major regulator of vascular homeostasis and it maintains a balance between vasodilation and vasoconstriction, and inhibition and stimulation of smooth muscle cell proliferation and migration, as well as thrombogenesis and fibrinolysis. Endothelial dysfunction occurs when this balance is upset, causing damage to the arterial wall. Endothelial dysfunction is considered an early marker for atherosclerosis. Flow-mediated dilation (FMD) of the brachial artery, the intima-media thickness (IMT) of the carotid artery and the pulse wave velocity (PWV) have all been shown to be good surrogate markers of clinical atherosclerosis. Statins inhibit hepatic 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is responsible for the reduction of circulating low density lipoprotein (LDL) cholesterol beginning one to two weeks after starting therapy. In addition, statins inhibit the HMG-CoA reductase that is within endothelial cells, vascular smooth muscle cells and inflammatory cells within hours after the administration of statins.

Several studies have reported that the early improvement of endothelial function after treatment with a variety of statins occurs independently of a decrease in LDL. However, there is limited information on the effect of the dose of statins on endothelial function. Therefore, the present study investigated the short-term effect on the FMD, PWV and IMT based on the dose and duration of statin treatment in patients with moderate cholesterolemia.
Subjects and Methods

Patient population
We enrolled 51 patients with moderate cholesterolemia (total cholesterol 200-250 mg/dL) between January 2005 and November 2005. Their mean age was 60.0±8.4 years; 41% of the enrolled patients were male. The patients were randomly divided into two groups according to the dose of atorvastatin they received: 10 mg for 27 patients and 40 mg for 24 patients. The patients with hypertension and diabetes were included as being in a state to tolerate statin medication.

The exclusion criteria included patients with renal dysfunction (serum creatinine >150% of the upper normal limit), hepatic dysfunction (aspartate and alanine aminotransferase >200% of the upper normal limit), overt proteinuria, a clinically significant cardiovascular disease or any sign of peripheral artery disease, cardiac pathology (uncontrolled arrhythmias, atrial fibrillation and documented ischemic heart disease), and acute inflammatory reaction.

This study was reviewed and approved by our ethical committee; written informed consent was obtained from all individuals before enrollment into the study.

Study design
All the patients underwent evaluation of the FMD of the brachial artery, the carotid-radial PWV and the IMT of both common carotid arteries, as well as biochemical testing that included lipid profiles for the efficacy of lipid-lowering, C-reactive protein (CRP) for the assessment of inflammation, the hepatic and renal function and muscle enzyme evaluation for adverse events at baseline, one week and at eight weeks after treatment with atorvastatin.

Biochemical tests
At study baseline, venous blood samples were obtained from the patient’s antecubital veins, and these patients had fasted overnight. The lipid serum levels, liver enzyme levels and muscle enzyme levels such as creatine kinase (CK) and lactic dehydrogenase (LDH) were measured by routine methods. CRP measurements were performed by the Nephelometer (Dade Behring Inc, Newark, DE, USA) method.

Measurement of carotid-radial pulse wave velocity
After the blood pressure was measured, the PWV measurement was performed in a controlled environment. The carotid-radial PWV was determined by using an automatic device, the Sphygmocor apparatus (AT-CORMedical, Sydney, Australia), between the carotid artery and radial artery. As we reported previously, measurement was carried out at 20 cardiac cycles when the difference of the consecutive means during repeated measures was less than 0.5 m/s, then the mean data was used for the final analysis.

Measurement of carotid intima-media thickness
B-mode ultrasound measurements were performed with a 10-MHz linear-array transducer that was connected to a Vivid 7 echocardiograph (General Electronics Corp., Horten, Norway). The patients were examined in the supine position. The operator directed the sound beam perpendicular to the arterial surface of the far wall of the common carotid artery (CCA) to obtain two parallel echogenic lines, which corresponded to the blood-intima and media-adventitia interfaces. The right and left CCA IMT were measured at least 10 mm proximal to the bifurcation. The values of the maximum and mean IMT were automatically calculated using the programmed software (M’ATH, METRIS Co., Argenteuil, France). The presence of a plaque was evaluated in the carotid artery. The plaque was defined as a distinct area, with an IMT exceeding twice that of the neighboring sites, so an IMT >1.3 mm was consequently not included in the calculation of the carotid IMT.11

Measurement of flow-mediated dilation
FMD was assessed by 2-dimensional ultrasonography (Vivid 7, General Electronics Corp., Horten, Norway) of the brachial artery by a modification of the method of Corretti et al.12 Measurements were performed on the left arm with the subjects in the supine position after a 10- to 20-minute rest in a quiet dark room at a temperature of 22°C. The brachial artery was scanned longitudinally, just above the antecubital crease, using a 10-MHz probe. The diameter of the brachial artery was measured at the R wave of the electrocardiogram, and at the interface between the media and adventitia of the anterior and posterior wall. Hyperemia was induced by inflation of a pneumatic cuff to 230 to 250 mmHg for four minutes on the most proximal part of the upper arm; the maximum arterial diameter was then measured 45-60 seconds after sudden deflation of the cuff. The maximum diameter during hyperemia compared with the baseline diameter was used for analysis. We measured each diameter three times during two beat, and the mean data was used for final analysis. Measurement was done by an independent observer who remained blinded to the medication of the study. FMD was defined as the percent increase in arterial diameter during hyperemia, i.e., 100 × (diameter after hyperemia−baseline diameter)/baseline diameter.

Statistical analysis
The SPSS 12.0 (SPSS inc., Chicago, Illinois) statistical software package was used for all calculations. Data are presented as means ± standard deviations (SDs) for continuous variables and as percentages for the categorical
data. Differences between the treatment groups for the lipid profiles and other biochemical parameters, along with each of the parameters of endothelial function, were analyzed by the unpaired Student t-test and by the paired Student t-test before (baseline) and after (one week or eight weeks) treatment. Linear correlation analysis (Pearson) was used to test correlations between changes in the carotid-radial PWV and FMD, and change in the LDL-cholesterol after therapy. Categorical data and proportions were analyzed using the Chi-square test. A p<0.05 was regarded as statistically significant.

Results

Demographic characteristics

Table 1 presents the demographic characteristics of the study population. There were no differences in age or gender between the groups. In addition, there were no differences in the cardiovascular risk factors such as obesity and a history of smoking, hypertension and diabetes between the groups. Other biochemical parameters, including the lipid profiles, CRP, blood urea nitrogen (BUN), creatinine (Cr), aspartate/alanine aminotransferase (AST), LDH and CK, were not different on comparisons between the groups. However, the alanine aminotransferase (ALT) level in the 10 mg group was increased compared with that of the 40 mg group. In addition, the carotid-radial PWV, FMD and carotid IMT were not significantly different on comparisons between the two groups.

Change of lipid profiles and C-reactive protein

Total cholesterol, LDL-cholesterol and triglycerides were significantly decreased after statin therapy in both groups. The decreases were statistically significant after one week and the lowest concentrations were reached after eight weeks in both groups (Fig. 1); the differences of the changes in the 40 mg group were significantly higher than those in the 10 mg group (Fig. 2). However, the changes in the HDL-cholesterol and CRP were not statistically different after statin therapy (Fig. 1).

Change of parameters for assessment of adverse events

All of the biochemical parameters that were studied, including CK, BUN, Cr and AST, were unchanged after statin therapy. However, in the 40 mg group, the ALT was significantly increased over time, although no patient exhibited clinically relevant increases (≥3× upper limit of normal) (Fig. 3).

Change of flow-mediated dilation, pulse wave velocity and intima-media thickness

The FMD was significantly increased after a fixed dose of 10 mg or 40 mg atorvastatin at one week and eight weeks of treatment. The carotid-radial PWV was significantly improved only in the 40 mg group at one week and eight weeks. The carotid IMT was unchanged after statin therapy in both groups (Fig. 4). Although the difference in the change of the FMD was not significant in the 10 mg and 40 mg groups, the difference of the change of the carotid-radial PWV in the 40 mg group was higher compared to that in the 10 mg group (Fig. 5). In addition, there was no significant correlation between the difference of the change in the carotid-radial PWV and FMD and the LDL-cholesterol (Fig. 6).

Discussion

This study was the first to evaluate the effect of statin treatment on the FMD, IMT and PWV according to the dose and duration of treatment in patients with moderate cholesterol levels. The results of the present study demonstrated that improvement of FMD was related to the duration of statin treatment, and improvement of the carotid-radial PWV was related to the dose of statin treatment. The difference in the effects of statin treatment on the FMD of the brachial artery and the carotid-radial PWV can be explained by the
different characteristics of atherosclerosis, as well as the different sites of the artery that was assessed for the degree of atherosclerosis.

The reports on the relationship between lipid changes and the dose and duration of statin treatment have been inconsistent. Edwards et al.\(^1\) reported that there was at best only a weak relationship between the statin dose and cholesterol reduction in a dose-specific meta-analysis of lipid changes following statin treatment. By contrast, Saito et al.\(^2\) reported that rosuvastatin pro-

Fig. 1. Changes of the lipid profile and C-reactive protein (CRP) after 10 mg (left panel) and 40 mg (right panel) atorvastatin treatment at one week and eight weeks later. The total cholesterol and low density lipoprotein (LDL) cholesterol were significantly decreased after 10 mg and 40 mg treatment, but not the high density lipoprotein (HDL) cholesterol and CRP. *p<0.05. NS: non-significant.
duced good dose-related reductions in LDL-cholesterol. In terms of the duration of statin treatment, atorvastatin 80 mg lowered the LDL-cholesterol level at 30 days, with significant benefit observed by four months in the Pravastatin and atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 study. However, these early reported benefits with undergoing statin therapy are not consistent with the results of the Aggrastat to Zocor trial of statin therapy, which showed no significant difference in efficacy by four months. Our findings showed that the effects of statin treatment to lower LDL and total cholesterol were dependent on the dose and duration of statin treatment (Fig. 2). However, these findings might have been due to the short term duration of statin treatment, which was a potential limitation in our study.

Several studies have demonstrated a lipid-independent early effect of statin treatment on endothelial function in a variety of clinical settings. Some investigators have reported that the short-term lipid-lowering effects of statins were able to improve endothelial function after three days in patients with high cholesterol by decreasing oxidative stress. Furthermore, Omori et al. reported that a single-dose of cerivastatin increased the FMD at three hours, and this returned to baseline six hours later. A number of mechanisms have been proposed to explain the early effect of statins on endothelial function.
been proposed to explain these effects. One important pathway appears to be the effects of statins on nitric oxide (NO) production by the increased availability of endothelial NO synthase. Cerivastatin has shown a time- and concentration-dependent effect on NO release from endothelial cells in experimental models.

Fig. 4. Changes in flow-mediated dilatation (FMD) of the brachial artery, the carotid-radial pulse wave velocity (PWV) and intima-media thickness (IMT) of both common carotid arteries after atorvastatin 10 mg (left panel) and 40 mg (right panel). The FMD was significantly improved after atorvastatin medication one week and eight weeks later; this improvement was related to the duration of statin medication. The carotid radial PWV was significantly improved after only atorvastatin 40 mg medication at one week and eight weeks, and this improvement was related to dose of the statin medication. However, there was no significant change in the carotid IMT despite atorvastatin medication for eight weeks. *p<0.05. NS: non-significant.
The initial release of NO has been reported to occur within three minutes and this was dependent on the concentration, similar to that observed for the typical NO synthase activators (calcium ionophore and acetylcholine). In the present study, a fixed dose of atorvastatin at 10 mg or 40 mg resulted in significant improvement in the FMD at one and eight weeks. This finding suggests that the improvement of FMD might be related to the duration of statin treatment.

Another important consideration is that NO may play a role in regulating arterial stiffness. Matsuo et al. reported that the ankle-brachial PWV was markedly improved after short duration (four weeks) of cerivastatin treatment. The change in arterial stiffness following treatment with simvastatin may be greater in the peripheral arteries than in the central arteries. The preferential improvement in peripheral arterial stiffness suggests that statin treatment reduced vascular smooth muscle tone rather than altering the properties of the extracellular matrix. In our study, only the atorvastatin 40 mg treatment group showed an improved carotid-radial PWV at both one and eight weeks. This finding suggests that improvement of arterial stiffness might be related to the dose of statin treatment. In addition in the 40 mg group, a majority of the improvement observed in the FMD and carotid-radial PWV after eight weeks was also observed after one week. Therefore, these findings suggest that most of the improvements in the FMD and carotid-radial PWV occur early after the start of statin treatment.

Measuring the carotid IMT quantitatively assesses the arterial morphology, which may partially consist of intimal lesions and medial hypertrophy. Statins have been shown to delay the progression or even cause regression of the carotid IMT. In a carotid injury experimental animal model, statin administration for two weeks decreased intimal thickening and smooth muscle cell proliferation. In human studies, a reduction in the IMT was shown as early as six months after the onset of statin treatment, and aggressive statin treatment (e.g. atorvastatin 80 mg/day) resulted in a -0.063 mm/year reduction in the annual progression of carotid atherosclerosis. In our study, we did not observe a change in the carotid IMT because of the low dose.
and short term duration of statin treatment.

The limitations of this study include: First, because of the small number of patients and short duration of statin treatment in our analysis, the relationship between statin therapy and the reduction of CRP and the changes of the IMT may not have been observed. Large-scale, long-term follow-up studies are required in the future. Second, we cannot completely rule out the possibility that a change in blood pressure affected the results of the post-treatment PWV. It may have been better to measure the stiffness parameter $\beta$, which is a blood pressure-independent index of arterial stiffness, to avoid such a problem.

In conclusion, the present results suggest that improvement of the FMD of the brachial artery and the carotid-radial PWV following statin treatment might be related to the dose and duration of statin therapy. Such an effect of statin therapy may be independent of lipid lowering.

Acknowledgments

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REFERENCES