The Anti-Atherosclerotic Effects of Lipid Lowering with Atorvastatin in Patients with Hypercholesterolemia

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We investigated the lipid lowering and anti-atherosclerotic effects of atorvastatin in patients with hypercholesterolemia. Thirty patients were given atorvastatin 10 mg daily, and assessed for serum lipids, intima-media thickness (IMT), and brachial-ankle pulse wave velocity (ba-PWV) at the baseline, 6 months, and 12 months. Remnant-like particle-cholesterol (RLP-C), lipoprotein (a) (Lp(a)), and high-sensitivity C-reactive protein (hs-CRP) were measured in some patients at the baseline and at 6 months. Total cholesterol, triglyceride and low-density lipoprotein cholesterol were significantly decreased by 32%, 23% and 44% at 6 months, respectively, and these effects were sustained at 12 months. There was no change in high-density lipoprotein cholesterol. IMT at the baseline was 0.88 ± 0.16 mm and decreased to 0.76 ± 0.13 mm at 6 months, remaining at 0.75 ± 0.12 mm at 12 months. We did not observe any significant changes in ba-PWV. RLP-C and hs-CRP were significantly reduced from 7.3 ± 10.8 mg/dL to 4.3 ± 5.3 mg/dL and 0.075 ± 0.065 mg/dL to 0.039 ± 0.043 mg/dL at 6 months, respectively. There was no change in Lp(a). The observed decrease in IMT suggests that atorvastatin possibly improves atherosclerosis, in addition to the significant reduction of serum lipids.


Key words; Statin, Atherosclerosis, Intima-media thickness, Brachial-ankle pulse wave velocity

Introduction

A large-scale epidemiological study showed clinically that hyperlipidemia is one of the major risk factors for atherosclerosis and coronary heart disease1, 2. In addition, various large-scale clinical trials for primary and secondary prevention have proved that the treatment of hyperlipidemia by statins significantly reduces the incidence of coronary events2, 3, 4. Furthermore, aggressive lipid-lowering therapy with atorvastatin in stable coronary heart disease has been proposed to be at least as effective as percutaneous transluminal coronary angioplasty5. Recent studies have also elucidated the pleiotropic effects of statins6, 7. Evidence for these additional effects suggests that lipid-lowering therapy with statins possibly improves atherosclerosis.

In this study, we gave atorvastatin to patients with hypercholesterolemia to evaluate lipid-lowering and anti-atherosclerotic effects. This was achieved by measuring the intima-media thickness (IMT) of the common carotid artery and brachial-ankle pulse wave velocity (ba-PWV) as indicators of atherosclerosis, and high-sensitivity C-reactive protein (hs-CRP) as an inflammatory marker.

Subjects and Methods

The subjects were 30 patients with hypercholesterolemia (total cholesterol (TC) was greater than 220 mg/dL in patients without established coronary artery
disease (CAD) and 180 mg/dL in patients with CAD). All received medical treatment at Takeda General Hospital. Nineteen patients were men, 11 were women, and their mean age was 68 ± 11 years. The indication of drug therapy was determined according to the Japanese Atherosclerosis Society (JAS) new guidelines for the diagnosis and treatment of atherosclerotic cardiovascular disease in 2002.8,9). All patients were given atorvastatin 10 mg daily. Diet and concurrent drugs were not changed during treatment. Fasting serum lipids (TC, triglycerides (TG), and HDL-cholesterol (HDL-C)) were measured at the baseline, 6 months, and 12 months. LDL-cholesterol (LDL-C) was estimated by the Friedewald formula. IMT of the common carotid artery and ba-PWV were assessed using ultrasonography and plethysmography (FORM; Colin, Japan), respectively; at the baseline, 6 months, and 12 months. One experienced sonographer performed all B-mode ultrasound examinations. Measurements were made at the far wall of the distal common carotid arteries and reported as the average value for bilateral measurements. All studies were performed on a single ultrasound machine (Aloka ProSound 5500) using a linear array 7.5 MHz scan head. Fasting remnant-like particle-cholesterol (RLP-C), lipoprotein(a) (Lp(a)), and hs-CRP were measured for some patients at the baseline and 6 months.

Values are presented as the means ± standard deviation. We tested mean differences using paired Student’s t-test; a p value < 0.05 was considered statistically significant.

Informed consent was obtained from all study subjects for participation in this trial.

Results

Medical history at the baseline indicated that 18, 14, and 5 patients had ischemic heart disease (present if a patient had a history of angina pectoris or myocardial infarction), hypertension (defined as a history of treated hypertension or blood pressure as measured in the hospital exceeding 160 mmHg systolic and/or 95 mmHg diastolic), and diabetes (present if a patient had a history of diabetes or a fasting blood glucose concentration exceeding 126 mg/dL), respectively. Concurrent drugs for ischemic heart disease and hypertension were as follows: 17 patients taking a calcium channel blocker; 5 an AR receptor antagonist; 11 an ACE inhibitor; 5 a β-blocker; 1 a nitrate; and 3 a diuretic. No changes were made to concurrent drug regimens during atorvastatin treatment.

Regarding serum lipids, TC significantly decreased from 241 ± 40 mg/dL to 165 ± 32 mg/dL (p < 0.01) at 6 months and this effect was maintained at 12 months. TG significantly reduced from 139 ± 74 mg/dL to 107 ± 60 mg/dL (p < 0.01) at 6 months and this effect was also sustained at 12 months. HDL-C however, did not significantly change. LDL-C estimated by the Friedewald formula significantly decreased from 156 ± 40 mg/dL to 87 ± 32 mg/dL (p < 0.01) at 6 months, and this effect was maintained at 12 months. RLP-C significantly declined from 7.3 ± 10.8 mg/dL to 4.3 ± 5.3 mg/dL at 6 months (p < 0.05), but Lp(a) did not change. hs-CRP significantly decreased from 0.075 ± 0.65 mg/dL to 0.39 ± 0.43 mg/dL (p < 0.05) (Table 1).

IMT at the baseline was 0.88 ± 0.16 mm; this significantly decreased to 0.76 ± 0.13 mm at 6 months (p < 0.05) and was maintained at 0.75 ± 0.12 mm after 12 months (Fig. 1). At the baseline Ba-PWV was 1674 ± 408 cm/s, at 6 months 1715 ± 417 cm/s and 1749 ± 431 cm/s at 12 months; overall there was no significant change (Fig. 2).

| Table 1. Plasma levels of lipids and lipoproteins at baseline, and after 6 and 12 months of treatment with atorvastatin 10 mg, and plasma levels of Lp(a), RLP-C and hs-CRP at baseline and after 6 months of treatment. |
|---|---|---|
|   | baseline | 6 months | 12 months |
| TC (mg/dL) | 241 ± 40 | 165 ± 32** | 164 ± 27** |
| TG (mg/dL) | 139 ± 74 | 107 ± 60** | 97 ± 47** |
| HDL-C (mg/dL) | 57 ± 13 | 57 ± 15 | 53 ± 13 |
| LDL-C (mg/dL) | 156 ± 40 | 87 ± 32** | 91 ± 25** |
| Lp(a) (mg/dL) | 19.8 ± 15.3 | 19.5 ± 15.5 |  |
| RLP-C (mg/dL) | 7.3 ± 10.8 | 4.3 ± 5.3* |  |
| hs-CRP (mg/dL) | 0.75 ± 0.65 | 0.39 ± 0.43* |  |

*p < 0.05 vs baseline. **p < 0.01 vs baseline
Discussion

This study demonstrated the substantial treatment effect of atorvastatin in lowering TC from 241 ± 40 mg/dL to 165 ± 32 mg/dL and LDL-C (estimated by the Friedewald formula), from 156 ± 40 mg/dL to 87 ± 32 mg/dL. Accompanying this lipid-lowering effect, a significant reduction of IMT was observed.

IMT is currently considered an important index of atherosclerosis progression. O’Leary et al. outlined the evidence for the IMT value in predicting the incidence of cardiovascular events. It has been reported that baseline IMT can also predict coronary heart diseases such as angina or non-fatal myocardial infarction among Japanese, based on a 3.1 year mean follow-up of 287 diabetic patients. Several studies have reported IMT reduction by atorvastatin. In this study, we observed a significant reduction of IMT with atorvastatin treatment. Therefore, atorvastatin would be expected to prevent coronary events and their sequelae.

The mechanisms by which statins improve atherosclerosis may involve so-called pleiotropic effects such as the improvement of vascular endothelial function and stabilization of the vascular wall plaque, either independently of, or dependent on the lipid-lowering effect. Pravastatin treatment for patients with hyperlipidemia was reported to improve the endothelial function of the coronary artery, in addition to reducing serum cholesterol levels. In addition, reports show that statins improve endothelial function through increased production of nitric oxide by the vascular endothelium and through other pathways, which are independent of the lipid-lowering effect. Indeed, animal experiments have shown that a small amount of fluvastatin improved vascular endothelial function and suppressed plaque formation. Moreover, this study observed a significant decline in the inflammatory marker hs-CRP with atorvastatin. Since statins have been reported to have strong associations with hs-CRP reduction and prevention of coronary events, atorvastatin could exert its anti-atherosclerosis effect through a mechanism involving reduction of hs-CRP.

A high level of remnant is also currently reported to be a risk factor for coronary atherosclerosis. Fibrates have been shown to be an efficacious treatment for high remnant levels, and a recent study showed that atorvastatin also decreases remnant levels. Atorvastatin could be expected to have an anti-atherosclerosis effect, as we have shown that atorvastatin significantly reduced RLP-C in this study.

Regarding IMT, reduction was observed after 6 months of atorvastatin treatment, but no further reduction was observed at 12 months. Similar observations were made in the ASPS study: aggressive lipid lowering with atorvastatin in familiar hypercholesterolemia reduced IMT for one year, but less reduction of IMT occurred in the following year. Since IMT increases gradually in patients with hypercholesterolemia, these results suggest a strong effect on IMT reduction with lipid lowering by atorvastatin at an early stage, whereas at a later stage, IMT reduction by atorvastatin and IMT increases due to progression of atherosclerosis tend to balance out.

PWV can be measured easily with plethysmography, and is a good index of the progression or regression of atherosclerosis. Statin treatment has been found to improve PWV among patients with hyperlipidemia, although it has also been shown that atorvastatin increases PWV, and no change in ba-PWV was observed after atorvastatin treatment in our study. These variable results may reflect the influence of many factors on PWV, including blood pressure, age and cardiovascular drugs. In our subjects, 18 patients had a history of ischemic heart disease and 14 had hypertension, and the drugs taken by these patients might have affected PWV. Therefore, to detect changes in PWV with statin therapy, it will be necessary to perform a study under strictly controlled conditions.

Study Limitations

There are several limitations to this study: the sample size is relatively small, the mean IMT at baseline was 0.88 mm, which is not high enough to be considered atherosclerotic, and the study was not performed in a comparative manner.
Lipid Lowering with Atorvastatin

Conclusion

Thirty patients with hypercholesterolemia were given atorvastatin 10 mg for a year and assessed using IMT. Atorvastatin is suggested to have an effect in improving atherosclerosis, conjectured from a significant decline of IMT, in addition to its significant serum lipid-lowering effect.

References


