Impact of Lipid-Lowering Therapy With Pitavastatin, a New HMG-CoA Reductase Inhibitor, on Regression of Coronary Atherosclerotic Plaque —— A 3-Dimensional Intravascular Ultrasound Study ——

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Background Recent lipid-lowering trials have reported that statin therapy may retard progression or stimulate regression of human coronary plaque. In the present study volumetric intravascular ultrasound (IVUS) analyses were performed to investigate the effect of pitavastatin, a newly developed statin, on regression of human coronary plaque.

Methods and Results Eighty-two patients matched for age and gender from 870 consecutive patients undergoing IVUS guided percutaneous coronary intervention were retrospectively assigned to either lipid-lowering therapy (n=41; pitavastatin 2 mg/day) or control group (n=41; diet only). Serial volumetric IVUS analyses of a matched left main coronary arterial site were performed. A significant reduction in low-density lipoprotein-cholesterol (LDL-C) level of 33.2% (p<0.001) was observed in the pitavastatin group. Plaque volume index (PVI) was significantly reduced in the pitavastatin group (10.6±9.4% decrease) compared with the control group (8.1±14.0% increase, p<0.001). There were positive correlations between the percent change in the PVI and follow-up LDL-C level (r=0.500, p<0.001) and the percent change in LDL-C level (r=0.479, p<0.001).

Conclusion Lipid-lowering therapy with pitavastatin induced significant coronary plaque regression, associated with a significant reduction in the LDL-C level. The percent change in the PVI showed a significant positive correlation with the percent change in LDL-C level. (Circ J 2007; 71: 1678–1684)

Key Words: Atherosclerosis; Intravascular ultrasound; Plaque; Statins

Progression of coronary atherosclerosis may lead to various cardiac events (angina pectoris, acute coronary syndrome, death), which HMG-CoA reductase inhibitors (statins) have been shown to reduce.1–5 In addition, recent lipid-lowering trials have reported favorable effects of statins on reduction of coronary artery atherosclerosis.6–9 Pitavastatin (Kowa Company Ltd, Nagoya, Japan) is a novel, fully synthetic statin, which effectively inhibits HMG-CoA reductase and has a cholesterol-lowering effect. Pitavastatin has been used in Japan since 2003 and its clinical efficacy and safety have been demonstrated for patients with hypercholesterolemia.10 However, few human studies have been performed investigating the effect of pitavastatin on coronary atherosclerosis, so the purpose of this study was to investigate retrospectively whether lipid-lowering therapy with pitavastatin could induce a significant regression of coronary artery plaque in untreated segments of left main coronary artery (LMCA) after percutaneous coronary intervention (PCI), as assessed by 3-dimensional intravascular ultrasound (3D-IVUS) analysis.

Methods

Study Population
The study population consisted of 82 patients who underwent serial 3D-IVUS examinations of the LMCA with planned or acute primary PCI for the left anterior descending (LAD) or left circumflex (LCX) in the Aichi Medical University Cardiac Catheterization Laboratory. These patients were matched for age and gender from 870 consecutive patients undergoing IVUS-guided PCI between January 1, 2003, and December 31, 2005. Forty-one patients treated with 2 mg of pitavastatin once daily administered within 48 h of the initial PCI and a low-fat diet were enrolled as the pitavastatin group, and 41 patients treated with low-fat diet only, matched for age and gender, were enrolled as the control group. Study patients received dietary counseling according to the standards of the American College of Cardiology/American Heart Association.11 The patients in the control group were given the option of statin therapy if their low-density lipoprotein-cholesterol (LDL-C) levels did not decrease after follow-up. This study was approved by the local medical ethics committee and written informed consent was given by all patients.

Patients with the following criteria were enrolled: (1) serum total cholesterol (TC) level <250 mg/dl, (2) de novo
and no significant plaque (angiographic lumen diameter stenosis <30%; “worst view” visual assessment) in the LMCA, (3) serial high-quality IVUS studies of the entire LMCA, (4) calcification not limiting quantitative assessment of vessel cross-sectional area (<75° total arc of calcium), and (5) no PCI in the LMCA or in the very proximal site of the LAD or LCX coronary arteries (these PCIs could have affected the LMCA plaque). Patients with any of the following were excluded: (1) failed PCI, (2) administration of lipid-lowering drugs before enrollment, and (3) renal or hepatic dysfunction.

The follow-up coronary angiography and IVUS measurements were performed 6 months after the initial procedure.

**Clinical Data and Coronary Risk Factors**

Patient demographics, coronary risk factors, and results of laboratory tests of patients with IVUS examination were recorded. All laboratory tests were performed at baseline and at follow-up as part of the clinical routine and were analyzed in the central laboratory of Aichi Medical University. Coronary risk factors including hypertension, diabetes mellitus (defined by medical history and oral glucose tolerance test), and history of smoking were noted.

**IVUS Imaging Protocol**

A mechanical IVUS imaging catheter (40-MHz, 2.5F, Cardiovascular Imaging System; Boston Scientific Corp, Natick, MA, USA) was used. All IVUS examinations were performed after intracoronary injection of isosorbide dinitrate to prevent catheter-induced spasm. The IVUS catheter was introduced over a 0.014-inch guidewire and positioned as distal as possible in one of the left coronary arteries, and withdrawn automatically using a motorized pullback device (0.5 mm/s). The IVUS images were recorded on S-VHS videotape and sent to Aichi Medical University Analysis Center for off-line quantitative analysis.

**IVUS Analysis**

Exact matching of the target site on the baseline and follow-up IVUS images was ensured by using side-by-side comparison of the serial IVUS video sequences, together with information of the pullback speed, the operator’s recorded comments (on videotape), and characteristic calcifications, vascular and perivascular landmarks, and plaque shapes. Series of cross-sections spaced exactly 0.2 mm apart were analyzed by the off-line system. For each cross-sectional image, the vessel area was measured by tracing the leading edge of the adventitia, and the lumen area was measured by tracing the leading edge of the intima. Vessel volume and lumen volume were measured using an algorithm based on Simpson’s rule. Plaque volume was calculated as vessel volume minus lumen volume. Volumetric analysis was performed with a Netra 3D-IVUS system (ScImage, Los Altos, CA, USA) throughout the LMCA. Quantitative analysis was performed by an independent, experienced IVUS investigator who was unaware of the patient groups and the angiographic result after patient selection. Volume index (VI) was calculated by averaging each volume, and each VI was defined as volume divided by the measured length for the vessel (VVI), the lumen (LVI), and plaque (PVI).

The change in PVI was defined as follow-up minus baseline PVI. The percent change in PVI was defined as (the change in PVI divided by baseline PVI)×100.

**Statistical Analysis**

Statistical analysis was performed with Stat View 5.0 (SAS Institute, Cary, NC, USA). Quantitative data are presented as mean±SD. Differences between 2 groups with or without statin treatment were assessed with the chi-square test for categorical variables and with unpaired Student’s t-test for continuous variables. Differences in continuous variables between baseline and follow-up were assessed with paired Student’s t-test. Percent changes from baseline for all lipid parameters and VI were tested using a 1-sample t-test. Correlations between the percent change in each VI and the lipid parameters were analyzed by linear regression analysis and correlation coefficient. In all tests, a value of p<0.05 was considered statistically significant.

**Results**

**Baseline Characteristics**

There were no significant differences in the distribution of patients with coronary risk factors or in the clinical characteristics of both study groups (Table 1). There were no serious cardiovascular events, including myocardial infarction, unstable angina, or death, in either group.
Table 2 Lipid Profile at Baseline and Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Pitavastatin (n=41)</th>
<th>Control (n=41)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mg/dl)</td>
<td>208.0±24.7</td>
<td>203.3±17.5</td>
<td>0.322</td>
</tr>
<tr>
<td>Follow-up (mg/dl)</td>
<td>161.7±24.5*</td>
<td>203.4±17.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in TC (%)</td>
<td>–21.8±11.0*</td>
<td>0.6±11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mg/dl)</td>
<td>127.8±61.5</td>
<td>142.3±70.4</td>
<td>0.324</td>
</tr>
<tr>
<td>Follow-up (mg/dl)</td>
<td>125.3±52.1</td>
<td>145.2±66.3</td>
<td>0.135</td>
</tr>
<tr>
<td>Change in TG (%)</td>
<td>–6.4±42.2</td>
<td>10.4±52.4</td>
<td>0.703</td>
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<tr>
<td>HDL-C</td>
<td></td>
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<tr>
<td>Baseline (mg/dl)</td>
<td>46.0±12.3</td>
<td>48.2±10.9</td>
<td>0.402</td>
</tr>
<tr>
<td>Follow-up (mg/dl)</td>
<td>48.0±14.6</td>
<td>50.3±13.0</td>
<td>0.460</td>
</tr>
<tr>
<td>Change in HDL-C</td>
<td>6.0±18.5</td>
<td>6.3±23.9</td>
<td>0.945</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mg/dl)</td>
<td>132.5±20.0</td>
<td>126.9±20.3</td>
<td>0.206</td>
</tr>
<tr>
<td>Follow-up (mg/dl)</td>
<td>87.4±18.1*</td>
<td>124.2±18.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in LDL-C</td>
<td>–33.2±14.5†</td>
<td>–0.2±19.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*<p<0.001 vs baseline (paired t-test); †<p<0.001 (one-sample t-test).
HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

Table 3 Volume Parameters From 3D-IVUS Measurements

<table>
<thead>
<tr>
<th></th>
<th>Pitavastatin (n=41)</th>
<th>Control (n=41)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Average length (mm)</td>
<td>4.9±1.4</td>
<td>3.8±1.3</td>
<td>0.457</td>
</tr>
<tr>
<td>VVI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mm³/mm²)</td>
<td>24.0±4.9</td>
<td>23.9±5.7</td>
<td>0.983</td>
</tr>
<tr>
<td>Follow-up (mm³/mm²)</td>
<td>23.7±4.5</td>
<td>24.0±5.9</td>
<td>0.805</td>
</tr>
<tr>
<td>Percent change in volume (%)</td>
<td>–0.6±5.8</td>
<td>0.4±7.7</td>
<td>0.490</td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mm³/mm²)</td>
<td>14.3±4.1</td>
<td>14.5±4.4</td>
<td>0.850</td>
</tr>
<tr>
<td>Follow-up (mm³/mm²)</td>
<td>15.1±4.2*</td>
<td>13.8±4.4</td>
<td>0.190</td>
</tr>
<tr>
<td>Percent change in volume (%)</td>
<td>6.1±12.3</td>
<td>–3.6±15.7</td>
<td>0.003</td>
</tr>
<tr>
<td>PVI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mm³/mm²)</td>
<td>9.6±2.5</td>
<td>9.4±2.3</td>
<td>0.706</td>
</tr>
<tr>
<td>Follow-up (mm³/mm²)</td>
<td>8.6±2.5*</td>
<td>10.2±2.7*</td>
<td>0.010</td>
</tr>
<tr>
<td>Percent change in volume (%)</td>
<td>–10.6±9.4*</td>
<td>8.1±14.0†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*<p<0.01 vs baseline (paired t-test); †<p<0.01 (one-sample t-test); §<p<0.01 (one-sample t-test).
D, dimensional; IVUS, intravascular ultrasound; VVI, vessel volume index; LVI, lumen volume index; PVI, plaque volume index.

Lipid Profile
During the observational period, there were no adverse reactions and no patient was withdrawn from the pitavastatin group. Although no differences were found in baseline lipid profiles between the 2 groups, the pitavastatin group showed significantly lower values of TC and LDL-C compared with the control group at follow-up (p<0.001, for both). In the pitavastatin group, TC and LDL-C levels were respectively significantly decreased by 21.8% and 33.2% between baseline and follow-up (p<0.001, for both). No significant changes in these variables were observed in the control group (p=0.99, p=0.54). High-density lipoprotein-cholesterol (HDL-C) and triglyceride levels showed no significant differences between the 2 groups at baseline or at follow-up (Table 2). In the control group, 13 patients (32%) were given statin therapy after follow-up because their LDL-C levels did not decrease.

Volumetric IVUS Analysis
An average 3.9±1.4 mm of the LMCA was analyzed in both groups. Table 3 shows the baseline and follow-up volumetric IVUS analyses of the LMCA. At baseline, there were no differences between the 2 groups in VVI, LVI, and PVI. However, PVI was significantly lower in the pitavastatin group (8.6±2.5 mm³/mm) compared with the control group (10.2±2.7 mm³/mm) at follow-up (p=0.010).

PVI was significantly reduced in the pitavastatin group (10.6±9.4% decrease; p<0.001 vs baseline vs follow-up). On the other hand, it was significantly increased by 8.1±14.0% in the control group (p<0.001 for baseline vs follow-up). PVI, <p<0.01 for pitavastatin vs control at follow-up). LVI was significantly increased in the pitavastatin group (6.1±12.3% increase; p<0.01 for baseline vs follow-up), although it was not significant, but tended to decrease in the control group (3.6±15.7% decrease; p=0.06 for baseline vs follow-up). The percent change in LVI was significantly higher in the pitavastatin group than that in the control group (p=0.003). VVI showed no significant change in either group for baseline vs follow-up.

Relationship Between Cholesterol and Serial IVUS Data
In all patients (the pitavastatin and control groups), the percent change in PVI showed a significant positive correlation with follow-up LDL-C level (r=0.500, p=0.001; Fig 1A) and the percent change in LVI showed a significant negative correlation with follow-up LDL-C level (r=-0.259, p=0.019; Fig 1B).
Impact of Pitavastatin on Coronary Atherosclerosis

Fig 1. Correlation between follow-up low-density lipoprotein-cholesterol (LDL-C) level and the percent change in plaque volume index (PVI) (A), lumen volume index (LVI) (B) and vessel volume index (VVI) (C). Follow-up LDL-C <75 mg/dl are represented by white dots (A, B), which indicate regression of PVI and increase of LVI.

Fig 2. Correlation between the percent change in low-density lipoprotein-cholesterol (LDL-C) level and the percent change in plaque volume index (PVI) (A), lumen volume index (LVI) (B) and vessel volume index (VVI) (C).
LDL-C level ($r=-0.312, p=0.004$; Fig 2B). There was regression of the PVI and increase of the LVI in all patients with follow-up LDL-C <75 mg/dl (Figs 1A,B). However, there were no correlations between the percent change in VVI and follow-up and the percent change in LDL-C level (Figs 1C,2C). There was also no correlation between baseline LDL-C level and the percent change in PVI. HDL-C (baseline and follow-up values, and the percent change) showed no correlation with the percent change in each VI.

Fig 3 shows representative patients from both groups. Serial (baseline and follow-up) IVUS images are presented side by side. A significant regression of the plaque and enlargement of the lumen in the LMCA are observed in the pitavastatin-treatment patient, whereas a significant progression of the plaque and shrinkage of the lumen are observed in the control patient.

**Discussion**

The present study demonstrates that lipid-lowering therapy with pitavastatin, a novel statin, induced a significant regression of the coronary atherosclerotic plaque burden in the LMCA, as assessed by serial 3D-IVUS analysis. To our knowledge, this is the first investigation to use 3D-IVUS analysis to evaluate the effect of pitavastatin on regression of coronary atherosclerotic plaque in patients with coronary artery disease, although several previous IVUS studies have demonstrated that other statins can retard plaque progression or accomplish plaque regression.

The pitavastatin dose used in this study is the most common dose used clinically in Japan (ie, 2 mg once daily), but is still half of the maximum approved dose. This dose of pitavastatin still produced a significant reduction of the LDL-C level (33.2% reduction), which was equivalent to that of previous trials with other statins in Japan.

The PVI was significantly reduced in the pitavastatin group, and there were significant positive correlations between the percent change in PVI and both the follow-up LDL-C level and percent change in LDL-C level. In a recent observational study, von Birgelen et al reported a positive correlation between the mean LDL-C level (the mean between baseline and follow-up LDL-C levels) and the annual change in plaque + media size of the LMCA. That was the first important study to report a direct relationship between LDL-C and changes in plaque size, and suggested the LDL-C cutoff value of 75 mg/dl. However, that study did not address pharmacological intervention and so there was no evaluation of a potential correlation between the follow-up LDL-C level or the annual change in LDL-C level and the impact on annual change in plaque + media.
size. In the present study, the pharmacological intervention improved the lipid profile and there were significant correlations between follow-up, percent change in LDL-C level and percent change in the PVI. Interestingly, there was demonstration of regression of the PVI and increase in the LVI in all patients with a follow-up LDL-C <75 mg/dl (Fig 1). This observation, which was also obtained in a previous study, suggests that intensive lipid-lowering therapy provides greater protection against cardiovascular events than moderate lipid-lowering therapy, as several other studies have shown.21,22

A recent observational study showed a relationship between LMCA plaque progression and adverse cardiac events.25 Based on the data from the present study, we speculate that PVI regression by pitavastatin has the potential to reduce cardiovascular events.

Furthermore, the LVI was significantly increased in the pitavastatin group, and there were significant negative correlations between the percent change in LVI and follow-up LDL-C level and the percent change in LDL-C level. It has been reported that long-term lipid-lowering therapy with statins for 2 years increases the lumen area of both the aorta and carotid artery.26 In the present study, similar results were obtained in the LMCA, which is the largest segment in the entire coronary artery tree, although the follow-up period was shorter.

Pitavastatin did not influence vascular remodeling because VVI showed no significant change in the pitavastatin group, and no significant correlations were found between the percent change in VVI and follow-up LDL-C level and the percent change in LDL-C level. Therefore, these results suggest that lipid-lowering itself plays an important role in coronary artery plaque regression. In addition, the results also suggest that not only the percent change in LDL-C level but also follow-up LDL-C level after pitavastatin treatment is important for coronary artery plaque regression.

**Study Limitations**

The major limitation is that this is a retrospective study and the use of pitavastatin at the time of the intervention was not randomized. This study design may present a possible risk of selection bias in the study population. Unmeasured or variable confounders not included in this study may affect the decision on pitavastatin therapy and the long-term outcomes, although IVUS examination was performed in a blinded manner and there was no significant difference in patient backgrounds between the 2 groups.

Second, the number of patients with serial volumetric IVUS analysis was relatively small, and additional larger studies are required to confirm our observations.

Third, this study only assessed a portion of the coronary arterial tree. It is not known whether progression and regression of coronary plaque was uniform throughout the coronary arteries.

Fourth, the IVUS image acquisition was not ECG-gated, so systolic and diastolic movement may have hindered a rigorous volumetric analysis of the coronary arteries.

The mechanism of the beneficial effects of statin therapy on coronary atherosclerotic plaque regression is not fully understood. Possible mechanisms include a LDL-C lowering effect, pleiotropic effects such as antioxidative effects anti-inflammatory effects effects on impaired endothelial function and/or anti-thrombotic effects. Because inflammatory markers, such as high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-Ç, and monocyte chemotactrant protein-1, were not measured in the present study, the influence of these pleiotropic effects on coronary plaque regression cannot be assessed. However, some animal studies have indicated that pitavastatin produces pleiotropic effects on the coronary artery, similar to other statins. Hayashi et al have demonstrated in a rabbit model that pitavastatin impairs endothelial function, and retards the progression of atherosclerotic formation.27 Yokoyama et al have demonstrated that pitavastatin inhibits inflammation in porcine coronary atherosclerotic plaque.28 Therefore, pitavastatin may play a beneficial role in human coronary artery plaque regression independent of lipid-lowering action. Additionally, this study did not assess plaque composition or the change in plaque composition with IVUS radiofrequency data analysis or other modalities.

**Conclusions**

This study demonstrates that lipid-lowering therapy with pitavastatin induced significant coronary plaque regression associated with a significant reduction in the LDL-C level. The percent change in PVI showed a significant positive correlation and the percent change in LVI showed a significant negative correlation with the percent change in LDL-C level. To confirm these findings, the Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) trial, which will evaluate the effects of pitavastatin on coronary plaque regression in patients with acute coronary syndrome, is ongoing.

**References**


