Preprocedural Statin Administration can Reduce Thrombotic Reaction After Stent Implantation

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Background  It has been reported that stent deployment results in acute inflammation and platelet deposition as an acute phase reaction and smooth muscle cell (SMC) proliferation as a chronic phase reaction. Other studies have shown that statin therapy can reduce thrombosis as a pleiotropic effect. The present study was undertaken to examine whether preprocedural statin therapy can reduce the thrombotic reaction after stent implantation by using in-stent restenosis (ISR) tissue.

Methods and Results  The study group consisted of 45 consecutive patients (stable angina) with ISR who underwent directional coronary atherectomy (DCA). According to the histological findings, the patients were divided into 2 groups: those whose ISR tissue included thrombus and SMC (T group), and those whose ISR tissue included only SMC (S group). Just before DCA, serum markers were evaluated, including high-sensitivity C-reactive protein (hs-CRP), lipoprotein (a), plasminogen activator inhibitor-1 (PAI-1), fibrinogen, total cholesterol, triglyceride, high-density lipoprotein cholesterol, fasting blood glucose, and hemoglobin A1c. Preprocedural medications, including statins, were also evaluated. The values for hs-CRP and PAI-1 in the T group were significantly higher than those in the S group, and the rate of statin use in the T group was significantly lower than that in the S group. There were no significant differences in any of the other factors. Multivariate analysis revealed that preprocedural statin use and the PAI-1 level were significant independent variables affecting the histological findings.

Conclusion  Preprocedural statins, associated with the involvement of PAI-1, can reduce the thrombotic reaction after stent implantation. (Circ J 2008; 72: 232–237)

Key Words:  Atherectomy; Restenosis; Statin; Stent; Thrombosis

In-stent restenosis (ISR) is one of the major clinical problems after percutaneous coronary intervention (PCI), even in the drug-eluting stent (DES) era. In fact, DES can significantly reduce the incidence of late restenosis after PCI, but other clinical problems, such as late thrombosis,5–7 can occur after PCI therapy. It has been reported that some medications, including the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins), may be effective in reducing restenosis after stent implantation;8,9 however, there are few data concerning the histological ISR findings and medications in humans. Some animal data are available10–12 but an enormous gap exists between animal experiments on the one hand and information obtained from observations in humans on the other.

Several recent randomized studies have demonstrated the beneficial effects of statin therapy in patients with acute coronary syndrome.13–16 The non-lipid-lowering, pleiotropic effects of statins include improvement in endothelial function, as well as reductions in oxidative stress, inflammation and platelet activation.17,18 However, there are still only a few studies regarding the effects of statins in patients with stable angina.16,19 We have reported that in such patients statins can reduce persistent inflammation after PCI, which may lead to partial reduction of restenosis.20 However, the exact details of how statins benefit patients with stable angina undergoing PCI are still unclear.

Komatsu et al have revealed that in humans, after stent implantation, in the initial stage, local thrombus formation, adjacent to the stent struts, is gradually invaded by cellular components, such as macrophages, and then in the chronic stage proliferation of smooth muscle cells (SMC) is induced by platelets and macrophages.21 Several pathological reports have also revealed that stent deployment results in thrombus deposition as an acute phase reaction, and proliferation of SMC as a chronic phase reaction.22–24 Because preprocedural statins can reduce thrombosis as an acute phase reaction after stent implantation, the current study was performed to examine whether preprocedural statin therapy can affect the histological reaction after stent implantation, by using ISR tissue in patients with stable angina. Other factors regarding thrombosis were also evaluated.

Methods

Subjects and Study Design

Between January and September 2004, all patients with stable angina who successfully received a bare metal stent in the target lesion were included. At the time of stenting, all...
patients were scheduled for a 6-month follow-up angiogram regardless of symptomatic status. Patients were eligible for inclusion in the study if they had angina pectoris or objective signs of myocardial ischemia and ISR of a native coronary artery, with a stenosis diameter of 50–99% by visual assessment. All patients received ticlopidine (200 mg/day) for 2 months in addition to continued aspirin medication (100 mg/day).

Before stent implantation, we evaluated the lesion type (ACC/AHA type A/B1 or B2/C)\textsuperscript{25} length and diameter, and remodeling features, using intravascular ultrasound (IVUS) (Atlantis Pro, Boston Scientific, Natick, MA, USA) as procedural data. The remodeling index was defined as the vessel area at the site of the target lesion divided by the average vessel area of the reference segments proximal and distal to the target lesion. We defined positive remodeling as an index score >1.0\textsuperscript{26,27} We also used IVUS to evaluate mechanical procedural factors, maximal inflation pressure for stent implantation and the ratio of minimum stent area to proximal reference lumen area\textsuperscript{22}.

We evaluated the incidence of classical coronary risk factors, including hypercholesterolemia, hypertension, diabetes mellitus and smoking. Hypercholesterolemia was defined as treatment with medication or serum low-density lipoprotein-cholesterol level \(\geq 140\text{mg/dl}\), hypertension was defined as blood pressure \(\geq 150\text{mmHg}\) despite therapy for at least 3 months, diabetes mellitus was defined as patients with type 2 diabetes currently treated with hypoglycemic agents or having a history of diabetes, and smoking was defined as smoking at least 15 cigarettes per day\textsuperscript{28}.

We divided the ISR lesion into 2 patterns: focal and non-focal according to Cosgrave’s classification\textsuperscript{29} The focal ISR pattern was defined as \(\leq 10\text{mm}\) in length within the stent and the nonfocal pattern was defined as \(>10\text{mm}\) diffuse, diffuse proliferative, or occlusive lesion.

Serum markers, including high-sensitivity C-reactive protein (hs-CRP), lipoprotein (a), plasminogen activator inhibitor-1 (PAI-1), fibrinogen, total cholesterol, triglyceride, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, fasting blood glucose and hemoglobin A\textsubscript{1c} were measured immediately before stent implantation. Preprocedural medications, administered at least 1 month before stenting, including statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium antagonists, ß-blockers and anticoagulants, were also evaluated. Preprocedural medications were not changed during the study period in any of the patients. All patients gave written informed consent, and the institutional ethics committee approved the protocol.

**Coronary Atherectomy**

Patients with ISR that was detected on 6-month follow-up angiography underwent directional coronary atherectomy (DCA) using Flexicut DCA catheters (Guidant Corporation, Santa Clara, CA, USA). The debulking procedure was continued until the remaining in-stent neointimal thickness was \(<0.5\text{mm}\), as seen on IVUS (Fig 1). Immediately after removing the atherectomy samples from the patient, tissue specimens were taken and immersion-fixed in 10% neutral buffered formalin before being processed into paraffin-embedded blocks. Between 1 and 4 tissue cross-sections per specimen were cut and placed on each slide.

**Histological Classification**

Ten-micrometer-thick tissue sections were cut for each specimen and, after hematoxylin-eosin staining, the patients were divided into 2 groups: the T group consisted of patients whose ISR tissue included fibrin as remnants of previous thrombus, and SMC; and the S group consisted of patients whose ISR tissue included only SMC (Fig 2). The pathologists who classified the atherectomy specimens were unaware of the clinical features of the patients. The various serum markers and preprocedural medications were compared between these 2 groups.

**Statistical Analysis**

Results are expressed as mean±SD and as percentages for categorical variables. Categorical variables were compared by the chi-square test or Fisher’s exact test. Continuous variables were compared by the Mann-Whitney U-test.
Multivariate analyses were performed using the logistic regression model on Stat View 5.0 MDSU statistical software (SAS Institute, Cary, NC, USA). Statistic significance was assumed at p<0.05.

Results

Histological Findings

Among 188 consecutive patients with stable angina who underwent bare metal stent implantation, ISR occurred in...
Table 2 Serum Markers and Preprocedural Medications

<table>
<thead>
<tr>
<th></th>
<th>T group (n=14)</th>
<th>S group (n=31)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>206±38</td>
<td>187±44</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>167±74</td>
<td>147±63</td>
<td>NS</td>
</tr>
<tr>
<td>High-density lipoprotein-cholesterol (mg/dl)</td>
<td>44±12</td>
<td>47±11</td>
<td>NS</td>
</tr>
<tr>
<td>Low-density lipoprotein-cholesterol (mg/dl)</td>
<td>134±37</td>
<td>121±29</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>111±23</td>
<td>112±43</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.6±1.0</td>
<td>6.1±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/dl)</td>
<td>29±15</td>
<td>30±24</td>
<td>NS</td>
</tr>
<tr>
<td>hs-CRP (mg/dl)</td>
<td>1.6±1.25</td>
<td>0.6±0.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>346±96</td>
<td>322±72</td>
<td>NS</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1 (mg/dl)</td>
<td>62±28</td>
<td>23±13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>43</td>
<td>90</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ACEI or ARB use (%)</td>
<td>45</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium antagonist use (%)</td>
<td>36</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>Î2-blocker use (%)</td>
<td>14</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Anticoagulant use (%)</td>
<td>7</td>
<td>13</td>
<td>NS</td>
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</tbody>
</table>

 hs-CRP, high-sensitivity C-reactive protein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 3 Independent Variables Correlating With Thrombosis of ISR Tissue

<table>
<thead>
<tr>
<th>Variable</th>
<th>T group (n=14)</th>
<th>S group (n=31)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprocedural statin therapy</td>
<td>0.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.567</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1,2.

Discussion

This study demonstrates that preprocedural statin therapy correlates with no evidence of organized thrombosis in ISR tissue. Farb et al studied human coronary artery specimens obtained at autopsy and showed that local thrombus formation, adjacent to the stent, occurs as an acute phase reaction after stent implantation.22 Other pathological studies of longer-term coronary stenting (>30 days after implantation) in humans have shown that ISR tissue consists of SMC-containing neointima, occasional fibrin-rich thrombi and chronic inflammatory cells.31 It has been reported that mechanical arterial injury correlates with the grade of acute phase reaction, inflammation and thrombosis, and chronic neointimal growth, and that the ratio of stent area to the proximal reference lumen area is a useful marker of the grade of injury.22 In the present study, this ratio, calculated by IVUS, and the other mechanical factors were similar between the 2 groups (Table 1). Thus, the grade of arterial injury by stent implantation was considered to be almost similar in both groups. Therefore, we believe that preprocedural statin therapy can reduce thrombosis as an acute reaction after stent implantation in patients with stable angina.20 To our knowledge, this is the first report showing that statins have an antithrombotic effect after stent implantation, using ISR tissue retrieved from patients undergoing DCA. Moreover, in almost all of the previous pathological studies of coronary arteries after stent implantation in humans, the tissues analyzed were obtained at autopsy.21,22,30,31 Thus, the results presented in those previous reports may not be representative of patients who have received stents and have survived. Therefore, we believe our histological data regarding the pleiotropic effects of statin therapy on ISR tissues in humans are valuable. Several studies showing that statins have anti-thrombotic effects independent of lipid-lowering action23–24 may support our data.

Univariate analysis revealed that the thrombotic reaction in ISR tissue was significantly correlated with preprocedural...
al statin therapy, hs-CRP and PAI-1. Multivariate logistic regression analysis showed that only preprocedural statin therapy and PAI-1 were independently correlated with the thrombotic reaction in ISR tissue. We consider that, because of the interaction between preprocedural statin therapy and hs-CRP,41–43 hs-CRP was not an independent variable in the multivariate analysis. Experimental studies have already demonstrated that preprocedural statin therapy substantially reduces the extent of inflammatory cell accumulation in the ischemic myocardium, in association with preservation of coronary blood flow, which is attributed to a reduction in leukocyte adherence to the microvascular endothelium, secondary to a reduction in the expression of adhesion molecules on the endothelial monolayer, and increased bioavailability of nitric oxide.38 Moreover, our previous report also demonstrated that statins can reduce persistent inflammation after PCI in patients with stable angina.39

There are few multicenter studies evaluating the effects of statin on stable angina or acute coronary syndrome in the Japanese population, so we must await future results of some ongoing Japanese studies.39,40 However, many reports have revealed that the pleiotropic effects of statins may reflect a common mechanism for downregulation of thrombin-mediated events, in particular at the cellular level.41 Thus, some reports have shown that statins reduce the activity of PAI-1;42–44 however, Kroger et al have reported that atorvastatin does not affect PAI-145 so the effect of statin therapy on the PAI-1 level is still controversial. In our study, PAI-1 was an independent variable for thrombotic reaction after stent implantation, although the interaction of statin therapy and PAI-1 was weak. Accordingly, using medications that focus on decreasing the PAI-1 level may be a useful therapeutic option for reducing the thrombotic reaction after stent implantation.

Study Limitations

This study was not a prospective randomized trial and the number of study patients was small. Moreover, most trials have shown that statins have no or weak effects on the rate of restenosis.46–48 We certainly agree on the non-beneficial effect of statins on restenosis because our histological examination also showed that statins did not reduce the proliferation of SMC. However, they did reveal that statins have antithrombotic effects, even in ISR tissue, and may induce beneficial effects on thrombosis and thrombotic events after stent implantation. In the DES era, SMC proliferation after stent implantation has been almost solved and thrombotic events have become a major clinical problems. We will never know the effects of statins on the patients in this study who did not suffer from restenosis, but we believe it has given the valuable insight that statins can reduce thrombosis in human ISR tissue.

Conclusion

Our histological study reveals that preprocedural statin therapy, associated with PAI-1, can reduce the thrombotic reaction after stent implantation. Thus, we believe that statins may be effective for preventing thrombotic complications after stenting.

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