Effect of Statin on the Reference Segments after Bare-Metal Stent Implantation

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The lipid-lowering and pleiotropic effects of statins, including their anti-inflammatory actions, have led to the use of these drugs in the prevention of adverse cardiovascular events. Two clinical studies, 'Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL),' which used high-dose atorvastatin (80 mg/day), and 'A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID),' in which high-dose rosuvastatin (40 mg/day) was administered, demonstrated non-progression or regression of atherosclerosis after treatment, as determined by serial intravascular ultrasound (IVUS) [1,2]. Serial IVUS allows the highly detailed evaluation of neointimal hyperplasia after stent implantation and of changes in plaque volume in de novo lesions. Although many IVUS studies have examined the efficacy of drugs aimed at the treatment of atherosclerosis, including statins, there are few reports in which this modality was used to analyze the effects of statins on either plaque regression or vascular remodeling in non-stented reference segments. These arterial segments are rarely disease-free, typically have a significant plaque burden, and may also have undergone remodeling changes [3]. The IVUS study by Hong et al. [4] was one of the few to evaluate the effects of the usual dose of simvastatin on plaque regression and vascular remodeling in peri-stent reference segments following the implantation of a bare-metal stent (BMS) and is thus of particular clinical significance. A comparison between the main outcome of that study and the outcomes of previous studies would provide a better understanding of the different effects of the various types of statins on the reference segments, the levels of low-density lipoprotein cholesterol (LDL-C), and related parameters.

Hong et al. [4], in their retrospective analysis, reported that the usual dose of simvastatin did not inhibit plaque progression and lumen reduction, nor did it affect vascular remodeling in peri-stent reference segments in patients who underwent BMS implantation. In their comparison of simvastatin and non-statin treatment groups, the authors found no significant differences in the changes in mean plaque plus media (P&M), lumen size, or external elastic membrane (EEM) area between post-stenting and follow-up, at either the proximal or the distal edges of the stent. These results were slightly different from those of other studies. For example, in an earlier study by Jensen et al. [5], the effect of lipid lowering by simvastatin on coronary atherosclerotic plaques was investigated with respect to changes in EEM, P&M, and lumen volumes. In 40 male patients with hypercholesterolemia, ischemic heart disease, and a non-significant coronary artery lesion, a significant reduction in P&M volume of 6.3% ($p = 0.002$) was observed after 12 months of simvastatin treatment, whereas the 1.8% reduction in EEM volume was not significant; there were also no concomitant changes in lumen volume. Accordingly, the study's authors concluded that 12 months of simvastatin therapy resulted in significant plaque regression. Similarly, another study evaluated in-stent neointimal

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hyperplasia and the changes of plaques at non-stented sites after simvastatin treatment [6]. Although in this study, 12-month statin treatment did not prevent intimal hyperplasia, persistent plaques (-4.0 ± 4.0 vs. +1.6 ± 3.8 mm³/mm, -14% ± 10% vs. +6% ± 12%, $p < 0.05$) and intermediate plaques (-2.5 ± 3.0 vs. +1.0 ± 3.0 mm³/mm, -10% ± 8% vs. +9% ± 9%, $p < 0.05$) at non-stented sites decreased in the simvastatin-treated group, but increased in the control group. The findings of these three studies can be interpreted as follows. First, as the Hong et al. [4] also suggested, most previous studies involving serial IVUS examination after simvastatin therapy were not aimed at the assessment of vascular changes within the peri-stent reference segment. Second, to evaluate and understand the factors contributing to plaque regression, it is necessary to consider LDL-C levels, which are regarded as one of the most important factors determining the progress of an atherosclerotic plaque. In a prior serial IVUS follow-up study, follow-up LDL-C levels were the strongest predictor of changes in mean P&M area ($r = 0.469$; $p < 0.001$; 95% confidence interval, 0.003 to 0.006) [7]. In the study by Hong et al. [4], the mean follow-up level of LDL-C in the simvastatin-treated group was 92 ± 30 mg/dL, which was higher than the optimal level of < 70 mg/dL, defined in the ASTEROID study as the cut-off value for plaque regression. Therefore, the decrease in LDL-C achieved using 20 mg simvastatin would not be enough to cause plaque regression; rather, in reference segments, a higher dose of the drug or more effective statins would be needed to improve the reduction of LDL-C.

The other important factor in plaque reduction is the anti-inflammatory action of statins, as determined by decreases in C-reactive protein (CRP) levels. Inflammation plays an important role in atherosclerotic plaque progression, and the anti-inflammatory effects of statins have been well established in several studies [1,2,8]. A significant reduction in CRP in the simvastatin-treated group compared with the control group was noted by Hong et al. [4] Further investigation into how CRP reduction is related to plaque regression will be helpful in confirming this association. In addition, an intercorrelation analysis between plaque regression and LDL-C or CRP levels is needed.

In addition to the systemic factors such as LDL-C and inflammatory markers, the local factors, including flow dynamics, shear stress, and type of implanted stent, have been reported to influence the vascular responses of reference segments. Kaneda et al. [9] suggested that in-stent lumen patency influences the vascular responses of adjacent reference segments after BMS implantation. The authors found that the lumen area in the smaller in-stent minimal lumen area (MLA) group (MLA < 3 mm²) decreased significantly at the distal edge compared with the larger in-stent MLA group (MLA > 3 mm²). An evaluation of the degree of neointimal growth will provide insight into the changes occurring in persistent reference segments.

The rupture of a vulnerable plaque is the most important mechanism leading to an acute coronary syndrome. This potentially fatal event may be strongly related to the specific components of the plaque. Therefore, treatment options for stabilizing vulnerable plaques and therapeutic strategies to reduce plaque volume are drawing increasing attention. In an earlier serial virtual histology study using an IVUS, plaques were characterized as having a calcified, fibrotic, or necrotic core, and each plaque was examined after the administration of one of two types of statin therapy [10]. In that study, rosuvastatin treatment achieved a statistically significant decrease in necrotic core volume (15.5 to 13.0 mm³, $p = 0.015$) and an increase in fibrofatty plaque volume (4.5 to 5.9 mm³, $p = 0.017$), whereas the effects of simvastatin were not significant. This result leads to the conclusion that, besides an evaluation of plaque volume changes using gray-scale IVUS, a second diagnostic tool is needed to evaluate the changes in specific plaque components.

With the widespread use of percutaneous coronary intervention in the treatment of coronary artery diseases, IVUS evaluation of both the vascular changes following stent implantation and the effects of specific drugs, including statins, on stented and reference segments has come to play an important role in the current drug-eluting stent (DES) era. The effects of statins on reference segments after DES implantation remain to be investigated. **(Korean J Intern Med 2010;25: 353-355)**

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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