

Cosmic Effect of Rosuvastatin in COSMOS

Takeshi Adachi, MD; Fumitaka Ohsuzu, MD

Coronary atherosclerosis starts in the mid-20s in men and gradually progresses. When the coronary arteries are occluded more than 75%, effort angina can occur, so slowing the progression of coronary atherosclerosis is important for the secondary prevention of ischemic heart disease. If we can achieve sufficient regression of coronary atherosclerosis with medical therapy, we may avoid excessive intervention and be able to provide more conventional therapies for patients with chronic ischemic diseases.

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In this issue of the Journal, Takayama et al publish the results of the COSMOS study, the Multicenter Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin using Intravascular Ultrasound in Japanese Subjects.¹ This study showed $-5.1\% \pm 14.1\%$ reduction in plaque volume and $7.3\% \pm 15.6\%$ increase in lumen volume with rosuvastatin treatment (average dose, 16.9 ± 5.3 mg/day for 76 weeks) in Japanese patients with ischemic heart diseases. That result is comparable with the ASTEROID trial in the USA.² In the ASTEROID study, patients were treated with very high-dose rosuvastatin (40 mg/day) and $-6.7\% \pm 11.1\%$ reduction in plaque volume was obtained. Notably, a similar reduction in plaque volume was obtained with approximately half the dose of rosuvastatin, indicating the required high-dose statin therapy aiming the coronary regression in Japanese patients.

Previous reports showed decreases in coronary plaque volume with statins. The ESTABLISH study demonstrated 13% reduction in plaque volume with atorvastatin in patients with acute coronary syndrome (ACS),³ but COSMOS enrolled only 7.9% patients with unstable angina and no patients with acute myocardial infarction. The atherosclerotic region contains lipid-rich, yellow plaque in ACS and in such cases, lipid-lowering therapy with statins can reduce plaque volume much more effectively than in the white atherosclerotic plaques in patients with stable angina. Considering secondary prevention and treatment of chronic ischemic heart diseases, the reduction in plaque in stable regions might be a more important long-term effect of statin treatment. Further clinical studies without ACS cases are awaited to establish the effects of statins on the regression of stable coronary atheroma.

The COSMOS study also included patients receiving prior lipid-lowering therapy if the plasma low-density lipoprotein (LDL) levels were ≥ 100 mg/dl or the total cholesterol levels

were ≥ 180 mg/dl. Importantly, rosuvastatin can decrease plasma LDL levels to $-33.5\% \pm 16.1\%$ in patients receiving prior lipid-lowering therapy and to $-52.5\% \pm 9.6\%$ in those who did not. According to “the lower is better” theory, the effect of rosuvastatin on coronary plaques may be because of its stronger lipid-lowering effects. For that reason, strong statins, such as rosuvastatin and atorvastatin, have been in used in various trials for coronary regression. However, the regression of atherosclerosis with rosuvastatin cannot be simply explained by its effects in lowering plasma LDL levels in the COSMOS trial. Although rosuvastatin decreased plasma LDL levels more in the patients who did not receive prior conventional lipid-lowering therapy, the regression of plaque did not differ between those who did or did not receive prior lipid-lowering therapy. Moreover, the reduction in plaque volume and the reduction in the plasma LDL level were not significantly correlated. These results indicate that effects beyond lowering plasma LDL levels affected the regression of atherosclerosis in the COSMOS trial. Interestingly, rosuvastatin increased plasma high-density lipoprotein (HDL) levels to a similar degree in both groups ($+20.3\% \pm 23.9\%$ in patients receiving prior lipid-lowering therapy, $+18.3\% \pm 20.3\%$ in patient not receiving prior lipid-lowering therapy). The regression in total atheroma volume was weakly but significantly correlated with the plasma HDL level and LDL/HDL ratio. Thus, an increase in the plasma HDL level may be an important factor in the decrease in plaque volume by rosuvastatin. High-dose statins are required for regression of coronary atherosclerosis and we raise the question that pleiotropic effects of statins, especially those not related to lipid metabolism, might have affected the results of the COSMOS trial.

Metabolic disorders, inflammation, and oxidative stress are the most important factors promoting vascular diseases. In the Jupiter trial, rosuvastatin decreased cardiovascular events in elder people with high plasma levels of high-sensitivity C-reactive protein (hs-CRP) and the beneficial effect of rosuvastatin was associated with anti-inflammatory effects, as indicated by decreasing plasma hs-CRP levels.⁴ We previously reported that after exclusion of patients with statin treatment, plasma hs-CRP levels are associated with the extent of coronary stenosis in patients undergoing coronary angiography.⁵ These findings suggest that lowering plasma hs-CRP levels with statins significantly affects coronary atherosclerosis. In the COSMOS study, rosuvastatin did not significantly decrease the plasma hs-CRP level ($3,326 \pm 7,823$ at baseline vs $933 \pm 1,549$ ng/ml, $P=0.49$),

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Department of Internal Medicine 1st, National Defense Medical College, Tokorozawa, Japan

Mailing address: Takeshi Adachi, MD, Department of Internal Medicine 1st, National Defense Medical College, 3-2 Namiki, Tokorozawa 359-8513, Japan. E-mail: tadachi@ndmc.ac.jp

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which may be related to the large variation in the data. Other inflammatory factors may be also involved in coronary atherosclerosis, such as interleukin (IL)-1, IL-6, IL-18, TNF- α , MMP or osteopontin.⁶ Further analysis may be required to clarify the anti-inflammatory effects of rosuvastatin in patients with stable coronary atherosclerosis.

Although no direct evidence has been found, antioxidants effects of rosuvastatin might affect the regression of atherosclerosis. Statins are known to inhibit small G proteins, such as Ras, Rho, and Rac, by preventing isoprenoid modifications. A recent report by Rashid et al showed that the clinical relevant dose of statins could not inhibit Ras and Rho, but did effectively inhibit Rac1.⁷ Rac1 is assembled with NADPH oxidases, the major vascular oxidases, and the inhibition of Rac1 is involved in various cardioprotective effects associated with the reduction of reactive oxygen species (ROS). The modulation of coronary ROS levels by rosuvastatin may not only cause plaque regression, but also enlarge the lumen or preserve endothelial function. We previously reported that atorvastatin induced regression of atherosclerosis in the thoracic aorta (−14%), but not in the abdominal aorta (+2%), as assessed by magnetic resonance imaging during a 2-year follow-up.⁸ The different effects of statins on regression of atherosclerosis may be related to variable levels of ROS production in the vessel walls. ROS production per surface area is greater in the carotid and abdominal aorta than in the thoracic aorta in rabbits,⁹ where peroxynitrite may regulate vascular tonus.¹⁰ In the coronary arteries, endothelium-derived hydrogen peroxide is much more important for regulating vascular tonus than in the thoracic aorta.¹¹ Thus, the involvement of ROS in vascular tonus may be more prominent in the coronary arteries than in the thoracic aorta, which may affect the degree of regression with statin therapy. High-dose rosuvastatin decreased only 5% of the plaque volume, and 34.7% of patients were dropped from the trial, mostly because of laboratory data abnormalities. Additional therapies to modulate plasma HDL-levels, inflammation, and small GTPases, as well as excessive oxidative stress, may help to achieve the

ideal regression of coronary atherosclerosis in the future.

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