Treatment With Statin on Atheroma Regression Evaluated by Intravascular Ultrasound With Virtual Histology (TRUTH Study) — Rationale and Design —

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on Behalf of Kanagawa PTCA Conference Study Group

Background Many clinical trials have shown that 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) can significantly reduce the incidence of coronary artery disease in both primary and secondary prevention. A recent study showed that aggressive lipid-lowering therapy with statins could achieve regression of coronary artery plaque evaluated with gray-scale intravascular ultrasound (IVUS). However, the actual changes in coronary artery plaque composition produced by statin therapy have not been well delineated.

Methods and Results This study will be a prospective, open-label, randomized multicenter study of 160 patients with stable or unstable angina who have undergone percutaneous coronary intervention with Virtual Histology™ IVUS (VH-IVUS). Patients will be randomly assigned to either the pitavastatin or pravastatin group. After treatment for 24–40 weeks, VH-IVUS will be performed again in the same segment of the coronary artery. The primary endpoint will be quantitative changes in each of the 4 components measured by VH-IVUS.

Conclusion The treatment with statin on atheroma regression evaluated by intravascular ultrasound with Virtual Histology (TRUTH) study will be the first multicenter study using VH-IVUS to evaluate the effects of statins on changes in coronary artery plaque composition and the findings will clarify the mechanisms of coronary artery plaque stabilization. (*Circ J* 2009; 73: 352–355)

Key Words: Coronary artery disease; Plaque composition; Statins; Virtual Histology™ intravascular ultrasound (VH-IVUS)

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) revolutionized the treatment of hypercholesterolemia, and many clinical trials have shown that they can significantly reduce

the incidence of coronary artery disease (CAD) in both primary and secondary prevention.^{1–5} Furthermore, intensive lipid-lowering therapy significantly reduces the risk of coronary events compared with moderate lipid-lowering therapy.^{6,7}

Imaging studies of coronary artery plaque have contributed considerably to our understanding of the benefits of intensive lipid-lowering therapies. The REVERSAL trial⁸ evaluated the effects of statin on coronary artery plaque volume using gray-scale intravascular ultrasound (IVUS). Moderate lipid-lowering therapy with 40 mg of pravastatin did not halt plaque progression, but aggressive lipid-lowering therapy with 80 mg of atorvastatin did. The ASTEROID trial investigated the effect of aggressive lipid-lowering therapy with 40 mg of rosuvastatin on regression of coronary artery plaque,⁹ and in Japan, 10–20 mg of atorvastatin prevented further progression of coronary atherosclerosis,¹⁰ while the ESTABLISH study showed a regression of coronary artery plaque with 20 mg of atorvastatin.¹¹ Further study has been performed in a Japanese population, using IVUS to evaluate the effects of rosuvastatin on regression of coronary atherosclerosis.¹² However, those trials have only evaluated quantitative changes of coronary artery plaque using gray-scale IVUS.

Virtual Histology™ IVUS (VH-IVUS) (Volcano Therapeutics, Inc, Rancho Cordova, CA, USA) has been devel-

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Fig 1. Flow chart of the study timeline. CAG, coronary angiography; PCI, percutaneous coronary intervention; VH-IVUS, Virtual Histology™ intravascular ultrasound.

oped by the Cleveland Clinic.¹³ It captures and analyzes radiofrequency ultrasound signals and can provide real-time automated maps by classifying atherosclerotic plaque into the 4 basic tissue types of fibrous, fibro-fatty, dense-calcium, and necrotic-core. The accuracy of VH-IVUS is approximately 80–92% *in vitro*¹³ and approximately 87.1–96.5% *in vivo*.¹⁴

Pitavastatin has a powerful lipid-lowering effect and has been used in Japan since 2003 where its clinical efficacy and safety have been demonstrated for patients with hypercholesterolemia.¹⁵ Takashima et al used IVUS to demonstrate that 2 mg of pitavastatin induced significant coronary artery plaque regression associated with a significant reduction of low-density lipoprotein (LDL)-cholesterol (C).¹⁶ To confirm their findings, the Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) trial was performed to evaluate the effects of pitavastatin and atorvastatin on coronary artery plaque regression in patients with acute coronary syndrome (ACS).¹⁷ However, the effects are evaluated by gray-scale IVUS and it is unknown whether plaque composition or vulnerability was changed.

Because it is unclear whether there are changes in the composition of coronary artery plaque following statin therapy, the present study has been designed to use VH-IVUS to examine the effects of statins. Furthermore, 2 statins (pitavastatin and pravastatin) will be evaluated. As placebo-controlled trials of statins are no longer ethically acceptable, a comparator group receiving pravastatin will be included. Pravastatin was selected because the Japanese MEGA study found that its use contributed to the prevention of CAD.¹⁸

Methods

Study Design

The treatment with statin on atheroma regression evaluated by intravascular ultrasound with Virtual Histology (TRUTH) study will be a prospective, open-label, randomized multicenter study of 160 patients with stable or unstable angina who have undergone successful percutaneous coronary intervention (PCI) of the culprit lesion under IVUS guidance and have a plaque area $\geq 50\%$ proximal or distal to the PCI site. In addition, patients must have baseline LDL-C level ≥ 140 mg/dl or judged by a physician to require treatment with statins to manage coronary risk factors. Exclusion criteria include: (1) established treat-

ment with statins, (2) hepatic disorder, or AST (GOT) or ALT (GPT) greater than 2.5-fold the upper limit of normal, (3) renal dysfunction (serum creatinine ≥ 2.0 mg/dl), (4) history of a severe muscular disorder or CK (CPK) greater than 2.5-fold the upper limit of normal, (5) acute myocardial infarction within 24 h of enrollment, (6) failed PCI, (7) cerebrovascular accident within 1 month of enrollment, (8) concurrent or a history of malignant tumor within 5 years, (9) receiving LDL apheresis, (10) homozygous familial hypercholesterolemia, (11) established treatment with any of the following: cyclosporine, fibrate, nicotinic acid, colestyramine and probucol, or (12) ineligible in the opinion of the investigator.

The included patients will give written informed consent approved by the institutional ethical committee after PCI and then be randomly assigned to either the pitavastatin or pravastatin group. The randomization will be stratified by the status of their CAD (stable or unstable angina) and by institution. The supervising physician will administer the allocated drugs within 1 week of PCI with a starting dose of pitavastatin 2 mg/day or pravastatin 10 mg/day for the first 1–2 weeks. After safety evaluation, the dose will be increased 4 mg/day or 20 mg/day, respectively. The patients will continue taking the allocated drugs until the end of study, until certain endpoints have occurred, or when they decide to discontinue participation in this study. IVUS, coronary angiography (CAG) and laboratory determination will be performed at baseline and 24–40 weeks (**Fig 1**).

The enrollment of patients is planned between December 2005 and February 2008 or until enrollment has been completed. The planned study duration is December 2005 to December 2008. The study has been registered at University Hospital Medical Information Network (UMIN) (UMIN ID: C000000311).

IVUS Examination

IVUS will be performed at baseline after culprit lesion intervention and at the 24–40 week visit. IVUS data will be derived from the region of interest (ROI), defined as >5 mm distal to the stent (ROI 1) and/or >5 mm proximal to the stent (ROI 2), with a reproducible index such as side branches. After injection of 0.2 mg nitroglycerin, a 20-MHz, 2.9-F phase-array IVUS catheter (Eagle Eye Gold, Volcano Therapeutics) will be placed distal to ROI 1 and/or ROI 2. Pullback will be performed automatically at 0.5 mm/s to the proximal part of ROI. Exclusion criteria include: (1) bypass graft at the site of PCI, (2) previous PCI lesion at

the site where IVUS evaluation is planned, (3) IVUS plaque area <50% at a non-PCI site (>5 mm proximal or distal to the PCI site), and (4) lesion is ineligible in the opinion of the investigator.

IVUS Analysis

IVUS images recorded in DVD format will be analyzed at the core laboratory to assess the changes in volume of each of the 4 components measured by VH-IVUS and the quantitative changes of the coronary artery measured by gray-scale IVUS (ie, vessel area and volume, lumen area and volume, plaque area and volume).

Endpoints

The primary endpoint will be quantitative changes in each of the 4 plaque components measured by VH-IVUS.

The secondary endpoint will be quantitative changes in the coronary artery parameters measured by gray-scale IVUS (vessel area and volume, lumen area and volume, plaque area and volume) and evaluation of major adverse cardiac events (MACE) [cardiac death, Q-wave infarction, non-Q-wave infarction, target lesion revascularization and coronary artery bypass graft]. Furthermore, changes in serum lipid levels [total cholesterol (TC), LDL-C, triglyceride (TG), high-density lipoprotein (HDL)-C], plasma total platelet-activating factor acetylhydrolase (PAF-AH) and HDL-associated PAF-AH concentrations, high-sensitivity C-reactive protein (hs-CRP), lipoprotein(a) [Lp(a)], oxidized LDL (Ox-LDL), apolipoprotein (apo) AI and apo B will be evaluated.

Safety Monitoring

Safety will be evaluated at 1–2, 4, 8, 12, 16, 20, and 24–40 weeks after enrollment. The Assessment Committee of Effect will evaluate MACE and any other adverse events.

Sample Size Calculation

The main goal of this trial is to evaluate differences between 2 statins in terms of changes in the composition of coronary artery plaque measured by VH-IVUS, according to the impact of differences in lipid-lowering effects. At present, there is no information in the literature about the effects of statins on the composition of coronary artery plaque. Therefore, it is difficult to set the target number of patients to achieve the primary endpoint. The study group estimated the necessary sample size based on the assumption that changes in plaque composition are accompanied by changes in plaque volume. The percent change in plaque volume was estimated by a linear relationship between the percent change of plaque volume and LDL-C that was reported by Okazaki et al.¹ According to this formula, the percent change of plaque volume was –11.5% in the pitavastatin group and –5.3% in the pravastatin group accompanied by respective changes in LDL-C of –47.0% and –29.8%. Okazaki et al also reported that the standard deviation of the percent changes in plaque volume after statin therapy was 12.8%. Assuming these factors, the sample size required in this study is 69 patients in each group to achieve 80% power by a 2-sided 2-sample t-test at a significance level of 5%. Assuming 10% of patients drop out, the sample size per group will be 69/0.9=77 patients.

Data Management

Patient information, blood samples, and IVUS images will be coded with the identification number of this study

and the coded number for individual identification will remain blinded. Blood samples will be obtained after overnight fasting. Serum lipids, apolipoproteins, hs-CRP, Lp(a) and Ox-LDL levels will be measured at a central clinical laboratory (SRL Inc, Tokyo, Japan). Serum TC, LDL-C, HDL-C and TG levels will be measured by standard enzymatic methods. Ox-LDL levels will be measured by an enzyme immunoassay as previously described.^{19,20} Serum Lp(a) levels will be measured by a latex-enhanced turbidimetric immunoassay. Total PAF-AH and HDL-associated PAF-AH concentrations will be measured by an enzyme-linked immunosorbent assay according to previously described methods (BML Inc, Tokyo, Japan).²¹ IVUS and CAG images will be analyzed at the core laboratory.

Statistical Analysis

Primary Endpoints Changes in composition of coronary artery plaque measured by VH-IVUS will be evaluated using analysis of covariance including the baseline measurement as a covariate. When an adjustment for multiplicity of testing is considered, a closed testing procedure in which the test for each component of composition is performed in the order of necrotic-core, fibro-fatty, fibrous, dense-calcium, will be applied with a significance level of 5%. An analysis adjusting for factors of dynamic allocation will be performed.

Secondary Endpoints Quantitative changes in the coronary artery parameters measured by gray-scale IVUS (vessel area and volume, lumen area and volume, plaque area and volume) will be evaluated by a 2-sided 2-sample t-test.

Study Organization

Principal Investigator Ichiro Michishita, Division of Cardiology, Department of Internal Medicine, Yokohama Sakae Kyosai Hospita, Yokohama, Japan.

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Conclusion

The TRUTH study will be the first multicenter study using VH-IVUS to evaluate the effects of statins on the composition of coronary artery plaque. The group is investigating the relationship between changes in plaque composition and lipid levels in stable or unstable angina patients receiving lipid-lowering therapy with pitavastatin or pravastatin. Furthermore, the study group hopes to show the process of coronary artery plaque stabilization by statins and that these findings will clarify the mechanisms of prevention of CAD by statin therapy.

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Appendix 1

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