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Original article

Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound (PRECISE-IVUS Trial): Study protocol for a randomized controlled trial☆

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ABSTRACT

Background: Although the positive association between achieved low-density lipoprotein cholesterol (LDL-C) level and the risk of coronary artery disease (CAD) has been confirmed by randomized studies with statins, many patients remain at high residual risk of events suggesting the necessity of novel pharmacologic strategies. The combination of ezetimibe/statin produces greater reductions in LDL-C compared to statin monotherapy.

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HMG-CoA reductase inhibitors
Plaque
Intravascular ultrasound

Purpose: The Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound (PRECISE-IVUS) trial was aimed at evaluating the effects of ezetimibe addition to atorvastatin, compared with atorvastatin monotherapy, on coronary plaque regression and change in lipid profile in patients with CAD.
Methods: The study is a prospective, randomized, controlled, multicenter study. The eligible patients undergoing IVUS-guided percutaneous coronary intervention will be randomly assigned to receive either atorvastatin alone or atorvastatin plus ezetimibe (10 mg) daily using a web-based randomization software. The dosage of atorvastatin will be increased by titration within the usual dose range with a treatment goal of lowering LDL-C below 70 mg/dL based on consecutive measures of LDL-C at follow-up visits. IVUS will be performed at baseline and 9–12 months follow-up time point at participating cardiovascular centers. The primary endpoint will be the nominal change in percent coronary atheroma volume measured by volumetric IVUS analysis.
Conclusion: PRECISE-IVUS will assess whether the efficacy of combination of ezetimibe/atorvastatin is noninferior to atorvastatin monotherapy for coronary plaque reduction, and will translate into increased clinical benefit of dual lipid-lowering strategy in a Japanese population.

Introduction

Cardiovascular (CV) disease remains the leading cause of death and a major cause of disability affecting quality of life [1]. Increased levels of blood cholesterol are causally related to an increased risk of coronary heart disease (CHD). Consistent with global studies, the age- and gender-adjusted incidences of CHD have been shown to significantly increase with increasing low-density lipoprotein cholesterol (LDL-C) levels [2]. Also, the positive association between achieved LDL-C level and the risk of CHD has been confirmed by randomized trials of lipid lowering [3]. In recognition of the benefits of intensive lipid-lowering therapy, the US National Cholesterol Education Program published an update document, suggesting a lower optional therapeutic goal for LDL-C in high-risk patients [4].

However, despite current standards of care aimed at achieving targets for LDL-C with the use of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), many patients continue to experience CV events and remain exposed to a high "residual risk" of future acute coronary events. Therefore, additional novel pharmacologic strategies for the prevention of CHD remain essential, particularly for high-risk patients [e.g. diabetic, or with acute coronary syndrome (ACS)].

On the other hand, ezetimibe inhibits the absorption of biliary and dietary cholesterol from the small intestine by blocking the Niemann-Pick C1 Like 1 receptor. Its addition to statin therapy leads to further decreases in LDL-C levels by 12–14%, allowing a greater proportion of patients to reach their National Cholesterol Education Program goal [5–7]. IMPROVE-IT will determine whether the addition of ezetimibe to statin therapy, using ezetimibe/simvastatin, improves CV outcomes compared with simvastatin monotherapy in patients after ACS [8]. However, whether the additional LDL-C lowering achieved with the addition of ezetimibe to statin therapy will lead to stronger coronary plaque regression is currently unknown [9]. Also, whether the difference of lipid-lowering strategy (sole inhibition of cholesterol synthesis vs. combined inhibition of synthesis and absorption) would have an impact on the plaque progression/regression has been not well understood. Thus, the Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound (PRECISE-IVUS) trial was designed to evaluate the effects of ezetimibe (cholesterol absorption inhibitor) addition to atorvastatin (cholesterol synthesis inhibitor), compared with atorvastatin monotherapy, on coronary plaque regression and change in lipid profile in patients with CHD. The study will also assess whether the efficacy of combination of ezetimibe/atorvastatin is noninferior to atorvastatin monotherapy for plaque reduction.

Study design

Study protocol

PRECISE-IVUS will be a prospective, randomized, controlled, assessor-blind, multicenter study to evaluate the effect of ezetimibe addition to atorvastatin on coronary artery atheroma volume as measured by IVUS in patients with CHD. Patients who satisfy all criteria for inclusion will be enrolled after having undergone successful coronary angiography (CAG) or percutaneous coronary intervention (PCI) under IVUS guidance to treat an episode of ACS or stable CHD (Table 1). Exclusion criteria are listed in Table 2. According to the criteria, the eligible patients will give written informed consent and then be randomly assigned to receive either atorvastatin alone or atorvastatin plus ezetimibe (10 mg) daily using a web-based randomization software conducted at the Large-Scale Clinical Trial Promotion Unit of the Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University (Fig. 1). Minimization, a dynamic randomization method that can balance groups with respect to both the numbers in each treatment arm and the characteristics of each group, will be utilized in the PRECISE-IVUS trial [10]. The randomization will be stratified by 1) gender, 2) age, 3) history of hypertension, 4) history of diabetes, 5) history of peripheral arterial disease, 6) serum LDL-C level, 7) serum high-density lipoprotein cholesterol (HDL-C) level, 8) serum triglyceride (TG) level, and 9) statin pretreatment prior to study enrollment. The dosage of atorvastatin will be increased by titration within the usual dose range with a treatment goal of lowering LDL-C below 70 mg/dL based on Western lipoprotein management guidelines [11]. If LDL-C levels are still 70 mg/dL or above, the atorvastatin dosage may be increased up to a maximum dose. If the investigator finds it necessary to reduce the dosage because of an excessive decrease in LDL-C or occurrence of adverse events, the dosage may be reduced again to a minimum dose at the discretion of the participating physician. The participants will continue taking the

Table 1
Inclusion criteria.

1. Patients who agree to be enrolled in the trial giving signed written informed consent
2. Aged 30–85 years at the time of their consent
3. Patients who have been diagnosed as ACS or stable coronary heart disease
4. Patients who undergo CAG or PCI under IVUS guidance
5. Patients with LDL-C ≥100 mg/dL at the time of their consent

ACS, acute coronary syndrome; CAG, coronary angiography; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol.

Table 2
Exclusion criteria.

1. Patients with familial hypercholesterolemia
2. Patients treated with ezetimibe
3. Patients treated with fibrates
4. Renal insufficiency (serum creatinine ≥2.0 mg/dL)
5. Altered hepatic function (serum AST or ALT ≥ 3-folds of standard value in each institute)
6. Patients undergoing hemodialysis or peritoneal dialysis
7. Any allergy to atorvastatin or ezetimibe
8. Severe underlying disease
9. Lack of decision-making capacity
10. Patients recognized as inadequate by attending physician

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

allocated drugs until the end of study. Investigators will follow up the participants for 9–12 months at participating centers or general physician's clinics, and will conduct medical examinations and blood testing. IVUS and CAG will be performed at baseline and 9–12 months follow-up time point at participating cardiovascular centers. This study is approved by the Institutional Review Board or Independent Ethics Committee of all of the participating centers. The planned duration is between October 2010 and September 2014 and the enrollment period may be extended if necessary. This study has been registered at clinicaltrials.gov (NCT01043380), according to the statement of the International Committee of Medical Journal Editors.

IVUS acquisition and analysis

The PRECISE-IVUS trial uses IVUS to trace lumen and vessel border, and to calculate coronary atheroma parameters at baseline and after trial treatment. Investigators will be required to use the same IVUS imaging system [40–45 MHz mechanical rotational commercially available IVUS imaging catheter (Boston Scientific, Natick, MA, USA; Terumo Corp., Tokyo, Japan; Volcano Corp., Rancho Cordova, CA, USA) and console] for both the baseline and follow-up IVUS image acquisition. Before imaging, intracoronary nitroglycerin 0.1 to 0.2 mg was administered. The IVUS catheter was advanced into the PCI or non-PCI vessel as distally as possible and withdrawn at a pullback speed of 0.5 mm/s automatically. IVUS images will be recorded onto CD-R for later offline analysis. The images will be logged and qualitative IVUS analysis will be performed by 2 independent blinded experienced observers in the IVUS core lab at the Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University according to the Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Regression/Progression Studies [12]. IVUS exclusion criteria might include 1) calcified plaque, 2) any cross-sections with a recognizable non-uniform rotation distortion (NURD), 3) presence of external elastic membrane out of view, 4) loss of image due to bubbles, or 5) any other artifact that prevents complete analysis. Coronary atheroma parameters will be assessed by volumetric analysis with the echoPlaque3 system (INDEC Systems, Inc., Mountain View, CA, USA). Baseline and follow-up IVUS images will be reviewed side-by-side on a display, and the target segment will be selected. The target segment to be monitored will be determined in a non-PCI site (>5 mm proximal or distal to the PCI site) on the PCI or non-PCI vessel with a reproducible fiduciary index such as side branches, calcifications, or stent edges.

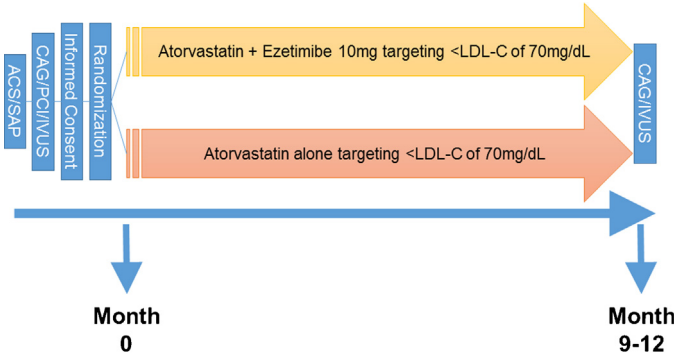

Fig. 1. Flow chart of the study timeline. Patients will be allocated to either atorvastatin monotherapy or atorvastatin/ezetimibe combination therapy. The target low-density lipoprotein cholesterol (LDL-C) level will be <70 mg/dL, in which atorvastatin is titrated by increasing the dosage up to a maximum dose daily. At the baseline and 9–12 month follow-up period, coronary angioscopy and intravascular ultrasound are performed. ACS, acute coronary syndrome; SAP, stable angina pectoris; CAG, coronary angiography; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound.

Endpoints

Based on an expert consensus document paper [12], the primary endpoint will be the absolute change in percent coronary atheroma volume from baseline to follow-up. The secondary endpoints will include 1) percent change in atheroma volume, 2) absolute and percent changes in lipid, glycemic, and inflammatory profile [total cholesterol, LDL-C, TG, HDL-C, HDL_2-C, HDL_3-C, remnant-like lipoprotein particles cholesterol (RLP-C), small dense LDL, oxidized LDL, free-fatty acid, apoA-I, apoB, apoC-II, apoC-III, lipoprotein (a), fasting insulin level, hemoglobin A1c, adiponectin, lathosterol, cholestanol, sitosterol, campesterol, high sensitive C-reactive protein (hsCRP)], 3) correlation between regression of coronary plaque and the lipid, glycemic, and inflammatory markers, 4) major adverse cardiovascular events [MACE; defined as cardiac death, Q or non-Q wave myocardial infarction, target vessel revascularization (PCI or coronary artery bypass grafting)], 5) all-cause death, and 6) any adverse incidents including changes in laboratory values. The above-mentioned laboratory measurements will be performed at a central clinical laboratory (SRL, Inc, Tokyo, Japan). LDL-C was measured using a direct LDL-C homogeneous assay.

Safety monitoring

Safety will be observed throughout the study, and be evaluated by regular medical examination and laboratory tests at 3, 6, and 9–12 months after enrollment. The Data and Safety Monitoring Committee (DSMC) will evaluate MACE and any other adverse events.

Sample size calculation

The effect of combination of atorvastatin/ezetimibe on coronary atheroma volume reduction, compared with atorvastatin monotherapy, has not been determined. The sample size calculation was thus performed based on the assumption that the effect of atorvastatin/ezetimibe combination therapy on the regression of coronary atheroma volume is not inferior to that of atorvastatin monotherapy, referencing the similar prior study accomplished in Japan, JAPAN-ACS study [13]. The nominal change in percent coronary atheroma volume in patients participating in the JAPAN-ACS study was $-6.3 \pm 6.1\%$ in an atorvastatin monotherapy group. We assumed that the mean and standard deviation of the nominal change in percent coronary atheroma volume in patients receiving atorvastatin/ezetimibe combination therapy were equal to those with atorvastatin monotherapy reported in the study. Based on the standard deviation in the atorvastatin monotherapy group, we

established a non-inferiority margin of 3%, and calculated 100 subjects in each group with an alpha level of 5%, a power of 80%. A key secondary objective was to determine whether atorvastatin/ezetimibe combination was superiority to atorvastatin monotherapy with respect to the nominal change in percent coronary atheroma volume.

Discussion

Attainment rate of target LDL-C levels and safety

The European guidelines for the management of dyslipidemia recommend aggressive lipid-lowering therapy targeting LDL-C <70 mg/dL in patients with CAD [14]. On the contrary, according to Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012 [15], the target LDL-C level for secondary prevention of atherosclerosis is currently <100 mg/dL. Despite the looser setting of target level of LDL-C, the attainment rate of these target LDL-C levels in patients treated with statins was less than 25% [16]. However, several studies demonstrated that statin/ezetimibe combination therapy (especially with strong statins) could help attain the guideline-recommended strict LDL-C goals [17]. Given these findings, the treatment strategies [atorvastatin/ezetimibe or atorvastatin monotherapy (dose titration)] planned in the PRECISE-IVUS trial will be expected to attain the LDL-C target levels of <70 mg/dL.

Difference in likelihood of plaque regression between ACS and stable angina

A significant regression in the coronary atheroma volume has been reported in previous studies using statins and other agents. Previous studies have suggested that statin-induced regression in coronary atherosclerosis appeared to be more prominent in patients with ACS [−13.1% to −18.1% in median percentage of change in total atheroma volume (TAV)] [13,18] than in patients with stable coronary artery disease (−0.4% to −6.8% in median percentage of change in TAV) [19,20]. Therefore, an association between the coronary plaque regression induced by statin therapy and patients' clinical presentation, such as stable coronary artery disease or unstable status, has been speculated. However, little has been studied regarding this association in a randomized study design prospectively. The PRECISE-IVUS trial will clarify this in a current clinical setting.

Clinical implication of the PRECISE-IVUS trial

Although a variety of factors could potentially influence the treatment effect of ezetimibe in the PRECISE-IVUS trial, a positive result will support the concept that combination of ezetimibe/statin could be an effective treatment especially for high-risk patients (e.g. individuals with high baseline LDL-C values, patients with diabetes, patients with established cardiovascular disease, and individuals with familial hypercholesterolemia). A positive result will also provide evidence supporting the concept that ezetimibe can be effective in patients who are unable to tolerate high-dose statins, those who may better tolerate a combination of low-dose statin plus ezetimibe, and those who do not achieve adequate LDL-C lowering despite high-dose statin use.

Given the combination effect of statin/ezetimibe previously demonstrated in the existing studies, whereas combined therapy with ezetimibe/simvastatin failed to show a significant difference in changes in intima-media thickness, as compared with simvastatin alone, in the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial [21], the SHARP (Study of Heart and Renal Protection) trial provided evidence for safe and effective lowering of LDL-C with a combination of ezetimibe/simvastatin among a wide range of patients with chronic kidney disease [22]. Furthermore, in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial conducted among patients with aortic stenosis, although there were no differences in preventive effect on major cardiovascular diseases, combination therapy was significantly superior to placebo in terms of preventive effect on ischemic heart disease [23]. Our IVUS findings from the PRECISE-IVUS trial would thus provide additional findings regarding possible underlying mechanisms of the above-mentioned beneficial effects of combination therapy on CV outcomes.

New cholesterol treatment guideline released by the American College of Cardiology/American Heart Association

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines has recently released the new cholesterol treatment guideline [24]. The new cholesterol treatment guideline emphasizes matching the intensity of statin treatment to the level of atherosclerotic cardiovascular disease (ASCVD) risk ("fire and forget" concept) and replaces the old paradigm of pursuing low-density lipoprotein cholesterol targets ("treat to target" concept). First of all, extrapolating the ACC/AHA recommendation into the current Japanese clinical setting, high-intensity therapy (≥50% LDL-C reduction), namely atorvastatin of 40–80 mg daily or rosuvastatin of 20–40 mg daily, has not been approved in the Japanese healthcare services provided by health insurance. Furthermore, the new guideline does not recommend treatment to reach a particular LDL-C, because the panel did not find any evidence of treating to a target. On the other hand, however, Boekholdt et al. showed that patients who achieve very low LDL-C levels have a lower risk for major cardiovascular events than do those achieving moderately low levels, supporting the concept of "the lower, the better" [25]. In addition, Nicholls et al. demonstrated that a direct relationship was observed between the burden of coronary atherosclerosis, its progression, and adverse cardiovascular events [26]. These data support the use of atherosclerosis imaging with IVUS in the evaluation of novel antiatherosclerotic therapies. A positive result of the PRECISE-IVUS trial could also lead to an early re-evaluation of the new ACC/AHA lipid management guidelines that endorse statins as the only recommended drugs for treating cholesterol-related CV risk.

Conclusion

PRECISE-IVUS will assess whether the efficacy of combination of ezetimibe/atorvastatin is noninferior to atorvastatin monotherapy for coronary plaque reduction, and will give us new insights into real-world information about lipid-lowering and suppression of coronary atheroma progression in Japan.

Disclosures

Hisao Ogawa has received remuneration for lectures from Bayer, Boehringer lngelheim, Daiichi Sankyo, MSD, Pfizer, and Takeda, and has received trust research/joint research funds from Bayer, Daiichi Sankyo, and Novartis, and has also received scholarship funds from AstraZeneca, Astellas, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Dainippon Sumitomo Pharma, Kowa, MSD, Otsuka, Pfizer, Sanofi, Shionogi, and Takeda. Masaharu Ishihara has received remuneration for lectures from MSD. The remaining authors declare no conflict of interest.

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Appendix A

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