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Original article

Efficacy of alirocumab for reducing plaque vulnerability: Study protocol for ALTAIR, a randomized controlled trial in Japanese patients with coronary artery disease receiving rosuvastatin

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ABSTRACT

Background: Although a recent clinical trial demonstrated that alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, significantly reduces the incidence of acute coronary events, the impact of alirocumab on plaque stabilization remains uncertain. The Efficacy of ALirocumab for Thin-cap fibroatheroma in patients with coronary Artery disease estImated by optical coherence tomogRaphy (ALTAIR) study will investigate the effect of alirocumab on thin-cap fibroatheroma (TCFA) in Japanese patients who underwent recent percutaneous coronary intervention (PCI).

Methods and design: ALTAIR is a phase IV, open-label, randomized, parallel-group, single-center study involving blinded optical coherence tomography (OCT) image analysis in Japanese adults hospitalized for PCI and having suboptimal control of low-density lipoprotein cholesterol (LDL-C) levels (>70 mg/dL) despite statin therapy. Patients will be randomized (1:1) to the alirocumab arm (alirocumab 75 mg every 2 weeks added to rosuvastatin 10 mg/day) or the standard-of-care arm (rosuvastatin 10 mg/day, with initiation and/or dose adjustment of non-statin lipid-lowering to achieve an LDL-C target of <70 mg/dL). OCT imaging will be conducted at baseline and at week 36 (post-treatment). The primary objective is to compare the alirocumab and standard-of-care arms regarding the change in TCFA fibrous-cap thickness after 9 months of treatment.

Conclusion: The outcomes of ALTAIR (ClinicalTrials.gov identifier: NCT03552432) will provide insights into the effect of alirocumab on plaque vulnerability following PCI in patients with suboptimal LDL-C control despite stable statin therapy.

Introduction

Although multiple countermeasures have been taken so far, cardiovascular disease remains one of the leading causes of death. For decades, the importance of low-density lipoprotein cholesterol (LDL-C) control has been repeatedly confirmed in Mendelian randomization studies, prospective cohort studies, and randomized controlled trials [1]. However, a recent study in Japanese patients with high cardiovascular risk reported that a substantial proportion of patients had suboptimal LDL-C control, highlighting the need for more potent lipid-lowering therapy in this population [2].

Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) have emerged as a novel treatment option for effectively lowering LDL-C levels by approximately 60% [3,4]. Recent randomized multicenter trials clearly demonstrated that use of a PCSK9 inhibitor was associated with a significantly reduced incidence of adverse clinical events in patients with high-

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risk stable coronary artery disease (CAD) [3] or acute coronary syndrome (ACS) [5]. Notably, supplementing statin therapy with PCSK9 inhibitors for aggressive lipid-lowering therapy was associated with significantly reduced incidence of acute myocardial infarction and unstable angina, events that are primarily triggered by plaque rupture due to increased plaque vulnerability.

Rupture-prone vulnerable plaque is characterized by a thin fibrous cap, a large lipid core, and macrophage infiltration near the fibrous cap, being referred to as thin-cap fibroatheroma (TCFA). Unlike other imaging modalities, optical coherence tomography (OCT) can detect TCFA in vivo because it facilitates the measurement of fibrous-cap thickness [6], which is one of the indicators of plaque vulnerability [7,8]. A recent clinical trial demonstrated that, among ACS patients, aggressive lipid-lowering therapy with statins is associated with significantly increased fibrous-cap thickness [9]. However, it remains unclear how vulnerable plaque is influenced by adding PCSK9 inhibitors to statins to achieve more aggressive lipid-lowering therapy. Therefore, we designed the Efficacy of ALirocumab for Thin-cap fibroatheroma in patients with coronary Artery disease estImated by optical coherence tomogRaphy (ALTAIR) trial. ALTAIR aims to clarify the efficacy of alirocumab, a PCSK9 inhibitor added to moderate-dose rosuvastatin, on TCFA fibrous-cap thickness in patients with CAD. In ALTAIR, fibrous cap thickness is estimated using OCT.

Materials and methods

Study design

ALTAIR is a phase IV, open-label, randomized, parallel-group, single-center study involving blinded OCT analysis in Japanese patients hospitalized for percutaneous coronary intervention (PCI) at Kobe University Hospital and who have elevated LDL-C values after PCI despite statin therapy. Approximately 24 patients with ACS or stable CAD will be enrolled to evaluate the effect of alirocumab added to rosuvastatin on TCFA fibrous-cap thickness, which will be measured using OCT. The planned duration of ALTAIR is 3 years, between June 2017 and September 2020, and the enrollment period may be extended if necessary.

ALTAIR is being performed according to the principles derived from the Declaration of Helsinki and from the International Conference on Harmonization Guidelines for Good Clinical Practice, as well as according to all applicable laws, rules, and regulations. The trial protocol was approved by the institutional review board of Kobe University Hospital. All patients who agree to participate are enrolled only after they have provided written informed consent. This study has been registered with ClinicalTrials.gov (trial identifier: NCT03552432), according to the statement of the International Committee of Medical Journal Editors.

Study population

ALTAIR employs the following eligibility criteria: age >20 years; PCI for ACS or stable angina pectoris; LDL-C levels >70 mg/dL despite statin treatment; OCT evaluation of TCFA characteristics in non-culprit, angiographically intermediate lesions causing 30%–70% diameter stenosis (Table 1). The ALTAIR exclusion criteria are listed in Table 2.

In this study, patients with prior statin therapy that did not involve rosuvastatin and with LDL-C levels >70 mg/dL at diagnosis will be switched to rosuvastatin 10 mg/day, whereas statin-naïve patients with LDL-C levels >70 mg/dL at the time of diagnosis will be started on rosuvastatin 10 mg/day immediately after PCI. In both situations, the patients are eligible to participate in ALTAIR if LDL-C levels remain >70 mg/dL at 2–4 weeks after rosuvastatin treatment initiation and if the treating physician determines it appropriate.

In ALTAIR, ACS is defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina. STEMI is defined as symptoms suggesting ischemia (e.g. chest pain or shortness of breath), with ≥1 mm of ST elevation in ≥2 consecutive chest leads or in ≥2 consecutive limb leads on electrocardiography or with a new left bundle branch block, and with elevated cardiac marker levels (cardiac troponin I levels above the 99th percentile upper reference limit) [10]. NSTEMI is defined as symptoms suggesting ischemia, with ST depression >0.5 mm (0.05 mV), negative T-wave (≥0.1 mV), or transient ST elevation ≤0.5 mm, and with elevated cardiac marker levels (as described for STEMI) [10]. Unstable angina is defined as symptoms suggesting ischemia without elevation of myocardial enzyme levels [10] plus one of the following: ST depression ≥0.5 mm or negative T-wave (≥0.1 mm); culprit coronary lesion responsible for ACS confirmed on diagnostic imaging (e.g. coronary angiography, multidetector computed tomography); new decrease in wall motion on cardiac ultrasonography; and evidence of reversible decrease in myocardial blood flow on pharmacological or exercise stress testing. Stable CAD is defined as ≥90% stenosis of a coronary artery confirmed on diagnostic imaging or evidence of reversible decrease in myocardial blood flow on pharmacological or exercise stress testing, with or without symptoms suggesting ischemia (except for STEMI, NSTEMI, and unstable angina) [11].

Study design

The study consists of a 36-week open-label treatment period (including post-treatment OCT imaging) starting within 4 weeks of PCI (Fig. 1). During the open-label treatment period, permuted-block randomization is employed to allocate patients to either the alirocumab arm or the standard-of-care arm (1:1). Randomization is performed using an Excel-based allocation system with stratification according to sex and serum LDL-C levels at baseline. Participants and investigators are not masked to the allocation, whereas OCT images are analyzed in a blinded fashion.

Patients in the alirocumab arm will receive subcutaneous alirocumab 75 mg every 2 weeks (Q2W) in addition to statin therapy (rosuvastatin 10 mg/day). The alirocumab dosage can be increased up to 150 mg Q2W to achieve an LDL-C target of <70 mg/dL. Patients in the standard-of-care arm will receive rosuvastatin 10 mg/day, with initiation and/or dose adjustment of non-statin lipid-lowering drugs to achieve an LDL-C target <70 mg/dL, based on 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias [12]; any non-statin lipid-lowering therapy will be continued at the same dose established after PCI unless modifications are required by the treating physician. If the physician finds it necessary to reduce the intensity of statin therapy because of an excessive decrease in LDL-C levels or occurrence of adverse events, the statin dosage may be reduced to a minimum. The participants are instructed to continue taking the allocated drugs until the end of the study. The participants will be followed-up for 9 months at Kobe University Hospital or at general physician clinics, where the investigators will conduct medical examinations and blood testing.

In both study arms, post-treatment OCT imaging of the PCI-treated same vessels will be conducted at the end of treatment period (i.e. at 36 ± 2 weeks). OCT image analysis will be performed by an independent imaging core lab (Kobe University Core Analysis Laboratory, Kobe, Japan) blinded to treatment arm allocation.

OCT image acquisition and analysis

OCT will be performed using the ILUMIEN OCT imaging system (Abbott Vascular, Santa Clara, CA, USA). A bolus intracoronary injection of nitroglycerin will be administered before OCT imaging.

Table 1
Inclusion criteria.

Inclusion criteria	
1.	Patients who underwent PCI for ACS or stable coronary heart disease
2.	Patients with LDL-C ≥70 mg/dL under daily 10 mg rosuvastatin
3.	Patients who have been had TCFA detected by OCT
4.	Patients aged ≥20 years old at PCI
5.	Patients who agree to be enrolled in the trial giving signed written informed consent

ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; TCFA, thin cap fibroatheroma.

Table 2
Exclusion criteria.

Exclusion criteria	
1.	Patients who have been treated previously with at least one dose of any anti-PCSK9 monoclonal antibody
2.	Patients had uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) between the time of PCI and randomization visit
3.	Known hypersensitivity to alirocumab or rosuvastatin
4.	All contraindications to alirocumab and/or rosuvastatin as displayed in the respective national product labeling for these treatments
5.	Known history of hemorrhagic stroke
6.	Currently under treatment for cancer
7.	Patients on lipoprotein apheresis
8.	Patients with severe liver or renal dysfunction
9.	Pregnant or breast-feeding women
10.	Considered by the investigator as inappropriate for this study for any reason

PCSK9, proprotein convertase subtilisin/kexin type 9; PCI, percutaneous coronary intervention.

Following a calibration adjustment, a Dragonfly JP OCT imaging catheter (Abbott Vascular) will be advanced distally to the target lesion over a 0.014-inch conventional angioplasty guidewire. After the catheter has been placed at the desired location, contrast media will be flushed through the guiding catheter at a rate of 2–4 mL/s for 3–6 s using an injector pump. When blood has been completely removed from the vessel segment to be scanned, the OCT scan will be initiated and conducted throughout the entire target lesion at a rate of 20 mm/s using an automatic pullback device. The OCT images will be digitally stored for offline analysis using a dedicated image review system (St. Jude Medical Inc., St. Paul, MN, USA) at the core laboratory (Kobe Cardiovascular Core Laboratory), which is blinded to arm allocation.

Serial OCT images at baseline and post-treatment will be reviewed side by side to match the target lesions based on the distance from landmarks (e.g. branching sites and calcifications). Calibration will be applied before OCT image analysis. For each target lesion, the minimum lumen area will be determined using an automated measurement algorithm and additional manual corrections, if necessary. Plaque tissue characterization will be performed using previously validated criteria [13]. Specifically, the lipid core will be identified and characterized as a region with poor signal intensity and diffuse borders. The fibrous cap will be identified as a signal-rich band overlying the lipid core. The minimum thickness of the fibrous cap will be determined using the following method [9]. Three candidate frames will be selected upon visual screening of all contiguous frames; fibrous-cap thickness, defined as the thickness of the signal-rich layer overlying the lipid-rich plaque, will be measured at the thinnest part of the fibrous cap in each frame; minimum fibrous-cap thickness will be determined as the smallest value of the fibrous-cap thickness measured in the candidate frames. The lipid arc in the target plaque will be evaluated as the largest arc in a signal-poor region with diffuse borders on the cross-sectional OCT image [14]. Lipid core length will be defined as the longitudinal length of the lipid-rich plaque (lipid arc ≥90°). The lipid core arc will be measured at 0.2-mm intervals throughout the lipid plaque to quantify the changes in plaque lipid proportion. The mean lipid core arc will be calculated for each lesion. Then, the lipid index will be calculated by multiplying the mean lipid core arc by the lipid core longitudinal length [15]. Macrophage accumulation will be defined as confluent or punctate, highly backscattering focal regions in the artery wall [16]. To quantify treatment-induced changes in macrophage accumulation, axial and circumferential macrophage distribution in the lesion will be graded every 0.2 mm, as follows: grade 0, no macrophages; grade 1, localized macrophage accumulation in a sector covering <30° of the lesion cross-sectional area; grade 2, clustered accumulation of macrophages in a sector covering ≥30° but <90°; grade 3, clustered accumulation in a sector covering ≥90° but <270°; and grade 4, clustered accumulation in a sector covering ≥270° [16]. For each target lesion, the overall macrophage accumulation grade will be obtained as the sum of grades of all lipid plaque sections analyzed. All quantitative and qualitative OCT parameters describing serial vascular changes will be compared between the groups.

Blood sample analysis

Serum levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride, non-HDL-C, and high-sensitivity C-reactive protein will be measured at weeks 0, 4, 12, 24, and 36, as reported previously [17]. Serum levels of apolipoprotein A-1, apolipoprotein B, lipoprotein(a), remnant-like particle cholesterol, and free PCSK9 will be measured at weeks 0 and 36 to investigate the potential relation between lipid profile modification and plaque stabilization. Additionally, the levels of interleukin-1β, interleukin-6, tumor necrosis factor-α, monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, matrix metalloproteinase-2,

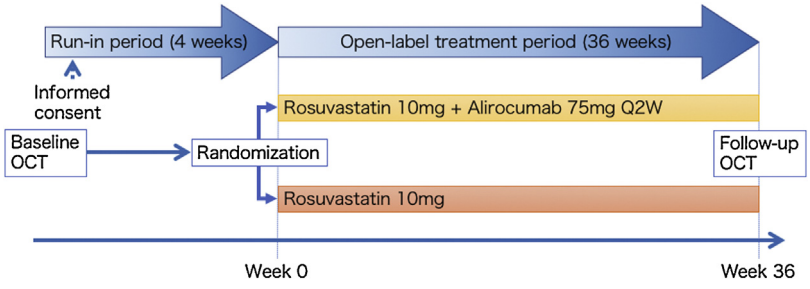

Fig. 1. Flowchart of patient enrolment, allocation, and analysis. OCT, optical coherence tomography.

and matrix metalloproteinase-9 will be measured at weeks 0 and 36 in order to elucidate the potential relation between plaque stabilization and inflammation.

Study endpoints

The primary endpoint of the study will be the change in minimum fibrous-cap thickness between baseline and the 36-week follow-up. Secondary endpoints will include the number of TCFA lesions at week 36, as well as the absolute change in mean lipid arc, lipid index, overall macrophage accumulation grade, and minimum lumen area between baseline and the 36-week follow-up. In addition, the present study will assess the incidence of cardiac death, myocardial infarction (defined based on an increase in levels of cardiac troponin I, according to the third universal definition of myocardial infarction) [10], ischemia-driven target-lesion revascularization, target-vessel revascularization, major adverse cardiac events (defined as the composite outcome of death, myocardial infarction, and ischemia-driven target-lesion revascularization), and adverse drug reactions during the follow-up period.

Safety monitoring

Safety will be observed throughout the study and evaluated via regular medical examination and laboratory tests conducted at weeks 4, 12, 24, and 36. All enrolled patients will be monitored and evaluated for major adverse cardiovascular events and any other adverse events during the study period.

Sample size calculation

The study is expected to enroll approximately 24 patients. The sample size calculation is based on the primary efficacy variable, namely the change in fibrous-cap thickness from baseline to week 36. A previous study [14] reported that the difference between 9-month eicosapentaenoic acid and rosuvastatin combination therapy and rosuvastatin monotherapy regarding the change in fibrous-cap thickness was 31.2 μm, with a standard deviation of 20 μm. Taking into consideration these previous observations, a sample size of 20 patients (10 in the rosuvastatin/eicosapentaenoic acid combination therapy arm and 10 in the rosuvastatin monotherapy arm) would have 90% power to detect clinically meaningful differences in treatment effect with a two-sided significance level of 5%. Assuming that the drop-out rate is 20%, ALTAIR aims to enroll 24 patients: 12 in the alirocumab arm, treated with rosuvastatin/alirocumab combination therapy; 12 in the standard-of-care arm, treated with rosuvastatin monotherapy.

Discussion

Compared to standard lipid-lowering therapy, aggressive regimens have been demonstrated to induce significantly more pronounced plaque regression. In the ASTEROID trial, Nissen et al. conducted serial intravascular ultrasound measurements and reported that high-intensity statin therapy using rosuvastatin 40 mg/day achieved average LDL-C levels of 60.8 mg/dL, resulting in significant regression of atherosclerosis over a 2-year follow-up [18]. Since then, many clinical trials reported significant plaque regression induced by intensive lipid-lowering therapy [19,20]. The clinical significance of plaque regression was confirmed in a meta-analysis of six intravascular ultrasound trials by Nicholls et al., which demonstrated a direct relation between progression of atherosclerosis and adverse cardiovascular events [21]. Thus, plaque regression by intensive lipid-lowering therapy is currently considered as an appropriate surrogate endpoint to evaluate the risk of future cardiovascular events in patients with suboptimal LDL-C control. Although most such evidence comes from studies on statin treatment, clinical evidence suggests that non-statin lipid-lowering therapy could offer comparable reduction of the risk of major vascular events [22]. Recently, the PRECISE-IVUS study reported that, compared to standard statin monotherapy, combination therapy with atorvastatin/ezetimibe was associated with a significantly greater regression of coronary plaque [23]. These data suggest that not only aggressive statin therapy, but also other lipid-lowering strategies can improve clinical outcomes by modifying coronary plaque through aggressive lipid-profile modification.

In addition to evaluating quantitative modifications, several studies investigated the qualitative impact of lipid-lowering therapy on plaque, such as the change in plaque vulnerability. Among various imaging modalities, intravascular OCT is a high-resolution imaging technique that has an incremental potential for plaque characterization, such as serial evaluation of the lipidic plaque [24]. At the same time, OCT is the only imaging modality that allows us to measure fibrous-cap thickness, which is thought to be a major factor in plaque vulnerability [6]. In a recent prospective, randomized OCT study enrolling 70 patients with unstable angina receiving atorvastatin, Kubo et al. demonstrated that, compared to low-intensity therapy (atorvastatin 5 mg/day), moderate-intensity therapy (atorvastatin 20 mg/day) provided a greater increase in fibrous-cap thickness of coronary plaques [9], which was associated with a greater decrease in serum LDL-C levels ($R = -0.450$; $p < 0.001$) and inflammatory biomarkers. These data suggest that, compared to standard therapy, aggressive lipid-lowering therapy can provide improved stabilization of unstable coronary plaque. Recently, the GLAGOV trial [25] examined the effect of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients with angiographic CAD and LDL-C levels of >80 mg/dL (or 60–80 mg/dL in the presence of one major or three minor cardiovascular risk factors). In this placebo-controlled study, the authors reported statistically significant plaque reduction after 76 weeks of evolocumab treatment, with greater plaque reduction and LDL-C lowering effect in evolocumab-treated patients than in placebo-treated controls. Also, ODYSSEY J-IVUS trial [26], which examined the effects of PCSK9 inhibition with alirocumab on progression of coronary atherosclerosis using intravascular ultrasound in Japanese ACS patients, is currently ongoing. These studies were, however, limited to the quantitative evaluation of the plaque, warranting further investigation to elucidate the potential qualitative plaque modifications afforded by PCSK9 inhibition. Therefore, we designed the ALTAIR study to compare the efficacy of alirocumab 75 mg Q2W added to rosuvastatin 10 mg/day with that of rosuvastatin 10 mg/day monotherapy in patients with CAD, with the primary outcome measure being the increase in OCT-measured TCFA fibrous-cap thickness, which is an indicator of plaque vulnerability.

Possible major limitations of the ALTAIR study will be the relatively small number of patients and the short interval duration for follow-up OCT. Another important limitation could be that there has not been compelling evidence demonstrating a direct relationship between the fibrous-cap thickness by OCT and adverse cardiovascular events. However, there has been much pathological research showing that the thickness of the fibrous cap is a major determinant of plaque vulnerability [7,27,28]. OCT is the only imaging modality that allows us to accurately measure fibrous-cap thickness in vivo [6]. Also, it is well known that OCT-based thin-cap fibroatheroma is associated with the presence of high-risk features evaluated by other imaging modalities such as virtual histology intravascular ultrasound [29], coronary computed tomography angiography [30], and magnetic resonance imaging [31]; all of which have significant relationships with future adverse clinical events [32–34]. Therefore, many investigators, including us,

currently consider that the thickening of the fibrous cap represents plaque stabilization in patients with CADs [9,14,35,36]. Further studies are needed to elucidate the clinical implications of the changes in fibrous cap thickness measured by OCT.

Conclusion

This study is the first to evaluate the efficacy of alirocumab/rosuvastatin combination therapy for increasing TCFA fibrous-cap thickness in CAD patients. The outcomes of the ALTAIR study will provide insights into the ability of alirocumab to stabilize TCFA over time in Japanese patients who recently underwent PCI and who, despite statin therapy, fail to achieve LDL-C target levels.

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Conflict of interest

There are no competing interests to disclose.

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