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Original article

Effect of alirocumab on coronary atheroma volume in Japanese patients with acute coronary syndromes and hypercholesterolemia not adequately controlled with statins: ODYSSEY J-IVUS rationale and design

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ABSTRACT

Background: Serial intravascular ultrasound (IVUS) imaging can be used to evaluate the effect of cholesterol-lowering on coronary atheroma progression and plaque volume, with evidence of potential incremental effects with more aggressive lipid-lowering treatments. Alirocumab is a highly specific, fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9). This study will investigate the effect of alirocumab on coronary artery plaque volume in Japanese patients with a recent acute coronary syndrome (ACS) and hypercholesterolemia while on stable statin therapy.

Methods: ODYSSEY J-IVUS is a phase IV, open-label, randomized, blinded IVUS analysis, parallel-group, multicenter study in Japanese adults recently hospitalized for an ACS and who have elevated low-density lipoprotein cholesterol (LDL-C) values [≥100 mg/dL (2.6 mmol/L)] at ACS diagnosis and suboptimal LDL-C control on stable statin therapy. Patients will be randomized (1:1) to receive alirocumab or standard-of-care (SOC). The alirocumab arm will receive alirocumab 75 mg every 2 weeks (Q2W) added to statin therapy (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day), with a dose increase to 150 mg Q2W in patients whose LDL-C value remains ≥100 mg/dL at week 12. The SOC arm will receive atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day, with dose adjustment to achieve LDL-C <100 mg/dL. Post-treatment IVUS imaging will be done at week 36 ± 2. The primary objective is to compare the effect of alirocumab versus SOC on coronary atheroma progression (percent change in normalized total atheroma volume) after 9 months of treatment.

Conclusion: ODYSSEY J-IVUS will provide insights into the effect of alirocumab on coronary atherosclerotic plaque volume in patients with a recent ACS and hypercholesterolemia while on stable statin therapy.

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Introduction

Patients with an acute coronary syndrome (ACS) are at high risk of cardiovascular death or recurrent ischemic events [1], and are recommended an early intensive statin therapy to reduce this risk based on evidence from multiple randomized controlled studies [2–4]. High-dose statins are generally safe and well-tolerated in predominantly Western populations [5]. They are efficacious in lowering low-density lipoprotein cholesterol (LDL-C), by 30–50% from pretreatment levels [6–8], and slow the progression of coronary atherosclerosis [9]. The incremental benefit of adding a non-statin lipid-lowering therapy to standard statin therapy in reducing the risk of cardiovascular events in ACS patients was first demonstrated in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [10]. Recently, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial reported a cardiovascular benefit of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor on top of statin therapy in patients with atherosclerotic cardiovascular disease and LDL-C $\geq$70 mg/dL [11]. In the Heart Institute of Japan PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER) trial in ACS patients with dyslipidemia, intensive lowering with pitavastatin plus ezetimibe demonstrated no greater cardiovascular benefit than pitavastatin monotherapy, except in the subgroup of patients with higher cholesterol absorption [12]. Guidelines published by the Japan Atherosclerosis Society (JAS) recommend lowering LDL-C to $<$100 mg/dL (2.6 mmol/L) in patients with established cardiovascular disease [13].

Epidemiological studies report lower cardiovascular and higher cerebrovascular event rates in Japanese versus Western populations [14,15]. The Reduction of atherothrombosis for Continued Health (REACH) investigators, in an analysis involving stable outpatients with or at risk of atherothrombosis, reported a correlation between Japanese ethnicity and lower cardiovascular risk compared with non-Japanese populations [16]. These Japanese-specific characteristics indicate the need for a specific outcome, or outcome surrogate marker, to establish the benefit of intensive LDL-C lowering in the Japanese population.

Intravascular ultrasound (IVUS) generates high-resolution images of the full thickness of the artery wall, providing the most accurate quantitation of plaque burden available currently [17]. Serial IVUS imaging has been employed to evaluate the effect of LDL-C-lowering strategies [9,18–22]. These studies demonstrated benefit in terms of reducing progression of coronary atherosclerosis and plaque volume, with evidence of potential incremental effects with more aggressive LDL-C-lowering regimens. Furthermore, a meta-analysis of six trials that used serial IVUS reported a direct relation between the burden of coronary atherosclerosis, its progression, and adverse cardiovascular events [23]. In Japan, IVUS forms part of the standard intervention procedure, and has been used in clinical trials to evaluate the effect of medical therapies on coronary atheroma progression [21,24–27]. The widespread use of IVUS in Japan is a unique characteristic of cardiovascular intervention practice in the country, and offers the opportunity for an effective imaging study involving country-wide samples.

Alirocumab is a highly specific, fully human monoclonal antibody to PCSK9. As monotherapy or on a background of other lipid-lowering treatment, alirocumab reduced LDL-C by 44–72% in patients with hypercholesterolemia [28–36]. In Japan, alirocumab is indicated for the treatment of patients with familial hypercholesterolemia or hypercholesterolemia who are at high cardiovascular risk and in whom statins are not sufficient to reduce serum LDL-C levels. The standard treatment dose is 75 mg every 2 weeks (Q2W), with a dose increase to 150 mg Q2W if the LDL-C reduction is insufficient. The ODYSSEY J-IVUS study will investigate the effect of alirocumab on progression of coronary atheroma volume in Japanese patients recently hospitalized for an ACS who have not achieved the recommended LDL-C level of $<$100 mg/dL at ACS diagnosis, as defined by the JAS [13]. The primary objective is to compare the effect of alirocumab versus standard of care on coronary atheroma progression [defined as percent change in normalized total atheroma volume (TAV)] after 9 months of treatment. The secondary objectives are to compare the efficacy of alirocumab versus the standard of care on secondary endpoints, including absolute change in percent atheroma volume (PAV) and in normalized TAV after 9 months of treatment; to evaluate the effect of alirocumab on LDL-C, apolipoprotein B, triglycerides, non-high-density lipoprotein cholesterol (non-HDL-C), lipoprotein(a), and HDL-C after 9 months of treatment; and to evaluate the safety and tolerability of alirocumab.

Methods

ODYSSEY J-IVUS is a phase IV, open-label, randomized, blinded IVUS analysis, parallel group, multicenter study in Japanese patients recently hospitalized for an ACS and who have elevated LDL-C values despite stable statin therapy. Approximately 200 patients from 40 study sites were to be randomized. The first patient was enrolled on November 15, 2016, and the last patient on 02 November, 2017 (n = 206 patients).

The study is being performed according to the principles derived from the Declaration of Helsinki and the International Conference on Harmonization guidelines for good clinical practice, and to all applicable laws, rules, and regulations. The protocol was approved by the institutional review boards of participating centers. All patients who agreed to participate were required to provide written informed consent. The study is registered at http://clinicaltrials.gov/NCT02984982.

Study population

Eligible patients are those aged $\geq$20 years who have been hospitalized for any ACS [ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina]; have LDL-C $\geq$100 mg/dL (2.6 mmol/L) at ACS diagnosis; have undergone IVUS imaging with at least 50% angiographic stenosis of the culprit vessel, within 1-week of ACS onset; and are negative to serum hepatitis B surface antigen, to total hepatitis B core antibody (or positive to hepatitis B core antibody and negative to hepatitis B DNA), and to hepatitis C antibody tests. Study exclusion criteria are listed in Table 1.

ACS patients who have already been on any statin therapy and whose LDL-C value is $\geq$100 mg/dL (2.6 mmol/L) at diagnosis will switch to atorvastatin $\geq$10 mg/day or rosuvastatin $\geq$5 mg/day (if not already on either of these), based on the investigators' judgment. Patients not previously taking a statin whose LDL-C is $\geq$100 mg/dL (2.6 mmol/L) at the time of ACS diagnosis, who start treatment with atorvastatin 10 mg/day or rosuvastatin 5 mg/day immediately after the diagnosis, and whose LDL-C value remains $\geq$100 mg/dL (2.6 mmol/L) (or $\geq$70 mg/dL, if the physician determines appropriate) 2–4 weeks later, will also be eligible to participate.

STEMI is defined as symptoms suggesting ischemia (e.g. chest pain or shortness of breath), with $\geq$1 mm of ST elevation in $\geq$2 consecutive chest leads or $\geq$2 consecutive limb leads on an electrocardiogram, or a newly occurring left bundle branch block, and elevated cardiac markers (troponin T $\geq$0.1 ng/mL or troponin I $\geq$0.04 ng/mL, or creatine phosphokinase $\geq$2 times the upper limit of normal). NSTEMI is defined as symptoms suggesting ischemia,

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