Atherosclerosis 239 (2015) 476–482

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Rosuvastatin may stabilize atherosclerotic aortic plaque: Transesophageal echocardiographic study in the EPISTEME trial

Yuji Ueno [a, b, *], Kazuo Yamashiro [b], Yasutaka Tanaka [a], Masao Watanabe [a], Nobukazu Miyamoto [a], Yoshiaki Shimada [b], Takuma Kuroki [b], Ryota Tanaka [b], Katsumi Miyauchi [c], Hiroyuki Daida [c], Nobutaka Hattori [b], Takao Urabe [a]

[a] Department of Neurology, Juntendo University Urayasu Hospital, Japan
[b] Department of Neurology, Juntendo University School of Medicine, Japan
[c] Department of Cardiology, Juntendo University School of Medicine, Japan

ARTICLE INFO

Article history:
Received 3 December 2014
Received in revised form
25 January 2015
Accepted 10 February 2015
Available online 16 February 2015

Keywords:
Stroke
Atheromatous aortic plaque
Rosuvastatin
Transesophageal echocardiography
Aortogenic brain embolism

ABSTRACT

Objective: Large atheromatous aortic plaques (AAPs) have been associated with ischemic stroke. There is little evidence to guide the therapeutic strategy for ischemic stroke associated with large AAPs. This study sought to analyze the temporal profile of AAPs after rosuvastatin therapy in Japanese patients with acute ischemic stroke.

Methods: The Efficacy of Post-stroke Intensive Rosuvastatin Treatment for aortogenic Embolic stroke (EPISTEME) trial was a prospective, randomized, open-label study. Acute ischemic stroke patients with dyslipidemia and AAPs ≥4-mm-thick on transesophageal echocardiography (TEE) were enrolled and randomly allocated to either the group treated with 5 mg/day rosuvastatin or the control group. The primary endpoint was the changes in volume and composition of AAPs on repeat TEE after 6 months. High-echoic plaque area was analyzed using binary images.

Results: A total of 24 Japanese patients (rosuvastatin 12; control 12) were included in the primary analysis. Rosuvastatin substantially reduced low-density lipoprotein cholesterol (LDL-C) compared to control (−42.1% vs. 1.4%, $P < 0.001$). Percent changes of high-echoic plaque areas were significantly increased in the rosuvastatin group, while they were decreased in the control group (65.8% vs −14.7%, $P < 0.001$). There was a significant linear correlation between percent increase in high-echoic plaque area and LDL-C decrease ($r = -0.434$, $P = 0.002$).

Conclusion: Treatment with 5-mg rosuvastatin for 6 months might induce atheromatous aortic plaque stabilization together with marked LDL-C reduction in Japanese patients with ischemic stroke, which could provide evidence on which to base the therapeutic strategy for aortogenic brain embolism.

1. Introduction

Stroke is a leading cause of death and disability worldwide, and atherosclerosis is the main cause of ischemic stroke. Large atheromatous aortic plaques (AAPs) ≥4 mm in thickness have been associated with ischemic stroke of unknown cause and stroke recurrence [1], [2]. In particular, advanced complex plaques, mobile plaques or ulcerated aortic plaques, are considered a high risk source of brain embolism [3]. Transesophageal echocardiography (TEE) has been the gold standard for evaluating AAPs, especially plaques with such morphologies, and many cross-sectional studies using TEE have contributed to obtaining great insights about AAPs [2–5]. We previously showed that AAPs with mobile or ulcerated morphology on TEE were closely associated with the ratio of low- (LDL-C) to high- (HDL-C) density lipoprotein cholesterol in unexplained stroke[5]. On the other hand, few studies have been conducted to assess serial variations over time of AAPs using repeat TEE, because TEE is a semi-invasive modality [6–8]. Thus, the effect of therapy on AAPs has not been studied using TEE.

HMG-CoA reductase inhibitors (statins) reduce cardiovascular events [9], [10]. Statins are also effective for primary prevention of ischemic stroke in patients with cardiovascular disease, as well as

* Corresponding author. Department of Neurology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo, Tokyo 113-8421, Japan.
E-mail address: yuji-u@juntendo.ac.jp (Y. Ueno).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.021
0021-9150/

for reducing the risk of ischemic stroke in secondary prevention, according to large-scale clinical studies [11], [12]. More importantly, statins have shown an anti-atherogenic effect on coronary and carotid atherosclerosis using diagnostic modalities, as well as a direct association with reduction of cardiovascular and cerebrovascular events [13], [14]. Rosuvastatin is one of the strongest statins to date, and it reduces the progression of atherosclerosis together with decreasing LDL-C[15–19]. Previous large-scale trials have shown the anti-atherogenic effect of rosuvastatin for coronary and carotid atherosclerosis [15–17], [19]. However, there is little evidence about the effects of rosuvastatin for aortic atherosclerosis in stroke patients.

The therapeutic strategy for aortogenic embolic stroke has so far been examined in a few studies that were retrospective and non-randomized [6], [20], [21]. The purpose of the present study was to carry out repeated TEE for Japanese patients with ischemic stroke to investigate the temporal profile of the size and composition of large AAPs in association with the improvement in the lipid profile after rosuvastatin therapy in a randomized, clinical trial.

2. Material and methods

2.1. Study design

This was a prospective, randomized, controlled, open-label trial conducted from August 2011 to September 2013 at Juntendo University Urayasu Hospital, a tertiary referral center. This study was conducted in accordance with the Declaration of Helsinki. The independent ethics committee of Juntendo University Urayasu Hospital approved this study (2011-048). All patients were given an explanation of the study, and written, informed consent was obtained for TEE and enrollment in the study from the patients or their relatives. This study was registered as 'Efficacy of post-stroke intensive rosuvastatin treatment for aortogenic embolic stroke (EPISTEME) trial' at http://www.umin.ac.jp/ctr/(UMIN000010548) [22].

2.2. Diagnosis of stroke subtype and indication for TEE

Patients with acute ischemic stroke within 7 days of onset underwent chest X-ray examinations and 12-lead electrocardiograms immediately after admission. Carotid ultrasonography, brain MRI, transcranial Doppler, and 48-h continuous electrocardiographic monitoring were performed within 24 h after admission. Based on the above stroke examinations, patients were initially classified into stroke subtypes using the criteria of the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) [23], and stroke patients with other determined etiology or undetermined etiologies were considered for TEE.

2.3. Eligibility criteria

Among stroke patients who underwent TEE, patients aged 20 years or older, having AAPs $\geq$4 mm in thickness on TEE, and diagnosed as having dyslipidemia, were eligible for the study. Reasons for exclusion were the presence of diseases requiring statin treatment, including coronary artery disease, presence of a serum LDL-C level >180 mg/dL, triglyceride level >400 mg/dL, familial hypercholesterolemia, secondary hypercholesterolemia due to hormonal disorders or other causes, undergoing LDL apheresis, treatment with cyclosporine, severe renal dysfunction or active liver disease, elevation of the creatine kinase level, confirmed malignancy or possible malignancy, contraindication to TEE (i.e., esophageal varix, diverticulum of the esophagus, congestive heart failure, or pneumonia), severe neurologic injury making it impossible to perform repeated TEE, and female patients who were pregnant, breast-feeding, or trying to become pregnant.

2.4. Risk factors

Atherosclerotic vascular risk factors were defined according to the previous literature: 1) hypertension, history of using antihypertensive agents, systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg at 14 days after stroke onset; 2) diabetes mellitus, use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin >6.4%; 3) dyslipidemia, use of antihyperlipidemic agents, serum LDL-C $\geq$140 mg/dL, HDL-C <40 mg/dL, or triglyceride $\geq$150 mg/dL; 4) current smoking; and 5) atrial fibrillation (AF), a history of AF or identification on 12-lead electrocardiography and electrocardiographic monitoring [3], [5], [22].

2.5. Sample size calculation

Alteration of AAPs before and after statin therapy has not been studied using TEE. According to the ORION and JART studies, we assumed that the percent change in LDL-C after therapy with 5 mg of rosuvastatin would be 40% [16], [19]. This decrease rate was relatively close to the percentage of LDL-C reduction by 20 mg of atorvastatin, as causing significant AAPs regression in 12% $\pm$ 12% on thoracic MRI [24]. We estimated that treatment with 5 mg of rosuvastatin would have an effect equal to that observed with 20 mg of atorvastatin. Thus, we presumed that a statistically expected change of AAPs and standard deviation would be 13% and 10%, respectively, between the two groups in primary endpoints in the present study. After considering dropouts, we calculated that 15 participants in each treatment group were needed for an alpha level of 5% and 80% power to show a significant difference between the two groups [22].

2.6. Biochemical blood tests

Laboratory data including serum lipid levels (LDL-C, HDL-C, LDL-C/HDL-C ratio, and non-HDL-C) were obtained by standard enzymatic methods at baseline and after 6 months of therapy.

2.7. TEE study

Initial and follow-up TEEs were performed at 0 (within 2 weeks after admission) and after 6 months of therapy. On TEE, AAPs were measured using the following protocol: at the point of origin of the left subclavian artery, four axial images of the aorta were captured every 1 cm distally, and images of AAPs $\geq$4 mm in thickness were obtained [22]. The examinations were performed by at least two experienced sonographers, and the images were recorded digitally. The obtained images were exported to TIFF files, and the National Institutes of Health open-access software ImageJ (version 1.43) software was used to measure the thickness and area of AAPs and the diameter of the aortic arch. Furthermore, the degree of aortic plaque with high echogenicity was determined using binary images, the protocols of which have been previously published [22]. This method was also used in the experimental study [25]. Briefly, exported TIFF images were converted to binary images and digitally level-adjusted using an intensity threshold for white and black pixels; thus, the white pixels in the aortic lumen represented high-echoic plaques. Low-echoic plaques were defined as the black pixel areas in the AAPs in the binary images. Comparing high-echoic plaque areas in the rosuvastatin and control groups, or at baseline and at 6 months in each group, the intensities of the aortic adventitia were standardized between each of their images. Using arbitrary units, intensities of high-echoic plaque areas in the