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Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma

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ABSTRACT

Background: The addition of highly purified eicosapentaenoic acid (EPA) to statin therapy prevents cardiovascular events. However, the impact of this treatment on vulnerable plaques remains unclear. The aim of this study was to assess the impact of adding EPA to a standard statin therapy on vulnerable plaques by serial optical coherence tomography (OCT).
Methods: Forty-nine non-culprit thin-cap fibroatheroma (TCFA) lesions in 30 patients with untreated dyslipidemia were included. Patients were randomly assigned to EPA (1800 mg/day) + statin (23 TCFA, 15 patients) or statin only (26 TCFA, 15 patients) treatment. The statin (rosuvastatin) dose was adjusted to achieve a target low-density lipoprotein (LDL) level of <70 mg/dL. Post-percutaneous intervention and 9-month follow-up OCT were performed to evaluate morphological changes of TCFAs. The EPA/arachidonic acid (EPA/AA) ratio and pentraxin-3 (PTX3) levels were also evaluated.
Results: Despite similar follow-up LDL levels, the EPA + statin group had higher EPA/AA ratios and lower PTX3 levels than the statin group. OCT analysis showed that the EPA + statin group had a greater increase in fibrous-cap thickness, with a greater decrease in lipid arc and lipid length. Macrophage accumulation was less frequently detected in the EPA + statin group than in the statin group at follow-up. When the patients were categorized according to their follow-up PTX3 tertiles, fibrous-cap thickness showed significant increase, and the incidence of macrophages accumulation decreased with lower PTX3 levels.
Conclusion: The concomitant use of EPA and rosuvastatin may stabilize vulnerable plaques better than the statin alone, possibly by suppressing arterial inflammation.

1. Introduction

Statin-based lipid lowering therapy reduces cardiovascular events and is recommended for patients with cardiovascular disease or coronary risk factors [1,2]. Some trials, however, have revealed residual cardiovascular risks even after the reduction of low-density lipoprotein cholesterol (LDL) to target levels [3,4]. According to recent studies, the addition of highly purified eicosapentaenoic acid (EPA) to statin therapy provides additional benefits for preventing cardiovascular events [5–7]. However, the impact of the additive EPA treatment with statin therapy on vulnerable plaques remains unclear.

Plaque rupture is the major mechanism of cardiovascular events, and plaque vulnerability is an important predictor of plaque rupture. Pathological studies have revealed that thin fibrous-cap thickness, large lipid pools, and macrophage infiltration near the fibrous-cap characterize vulnerable plaques [8,9]. Optical coherence tomography (OCT) is a feasible imaging technique for detecting thin-cap fibroatheromas (TCFAs) *in vivo* because of its high resolution [10–13]. In addition, arterial inflammation plays an important role in promoting plaque vulnerability, and high-sensitivity C-reactive protein (hs-CRP) and pentraxin-3 have been reported as useful markers of arterial inflammation [14–16].

The aim of this study was to assess the impact of EPA and statin therapy on the stabilization of vulnerable plaques in patients with

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untreated dyslipidemia, using serial OCT and serum inflammatory marker evaluations.

2. Methods

2.1. Study design

The study was designed as a randomized, open-label study to assess the impact of 9-month combined therapy using EPA and a statin on OCT parameters and serum inflammatory markers in patients with dyslipidemia. Patients who underwent percutaneous coronary intervention (PCI) for stable angina or acute coronary syndrome and having LDL levels >100 mg/dL without lipid-lowering therapy, were candidates for the study. Acute coronary syndrome (ACS) was defined as acute myocardial infarction (MI) or unstable angina pectoris. MI was defined as a recent symptom of ischemia with electrocardiogram abnormalities, depression or elevation of at least 0.1 mV in the ST segment and troponin T or I elevation. Unstable angina was defined as new-onset severe angina, accelerated angina, or angina at rest. Stable angina was defined as an absence of changes in the frequency, duration, or intensity of symptoms within the 4 weeks preceding the PCI [17]. Patients were excluded from the study if they (1) were already using statins or other lipid-lowering therapies, (2) had known hypersensitivity to statins or contrast, (3) had end-stage renal failure (serum creatinine [Cre] ≥ 2.0 mg/dL), (4) demonstrated hemodynamic and respiratory instability (e.g., cardiogenic shock, severe congestive heart failure), or (5) had terminal stage cancer or dementia (serious conditions that may compromise successful study participation).

After successful PCI to the culprit lesion, multi-vessel OCT examinations of the remaining non-culprit lesions with mild-to-moderate stenosis were performed to detect TCFAs. TCFA was defined as a plaque presenting with a fibrous-cap thickness <65 μm and a lipid arc ≥90° [18]. Finally, patients were enrolled in the study if they had TCFAs in non-culprit, mild-to-moderate stenotic lesions; the patients were randomly assigned to 2 groups: EPA + statin and statin only. The EPA + statin group patients received EPA (1800 mg/day) and rosuvastatin; the statin group received rosuvastatin alone.

Blood analyses and planned follow-up OCT examinations were performed 9 months after the index procedure, regardless of symptomology. During the study period, serum LDL levels were evaluated monthly, and the dose of rosuvastatin was adjusted to achieve a target LDL level of <70 mg/dL, in both groups. Also, they received similar dietary counseling until 1 month after the index procedure.

The ethics committee of Kobe University approved this study, and all enrolled study patients provided written informed consent to participate in this clinical trial.

2.2. Lipid profile and inflammatory markers

Serum LDL levels were evaluated monthly to adjust the dose of rosuvastatin in patients in both groups. Other lipid profiles and inflammatory markers were evaluated before the start of lipid-lowering therapy and 9 months after the PCI. The lipid profile also included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and EPA/arachidonic acid (AA) ratios. The extent of arterial inflammation was evaluated by determining hs-CRP and PTX3 levels.

2.3. OCT examination

To evaluate plaque characteristics, we performed multivessel frequency-domain OCT examinations at the time of the PCI and at the time of the 9-month follow-up angiography. In this study, OCT was performed in a standard fashion, as previously reported [19]. Briefly, a C7 Dragonfly™ catheter (LightLab Imaging, Westford, MA, USA) was advanced to the distal end of the target lesion over a 0.014-inch guide wire, followed by the infusion of contrast medium into the coronary artery from the guiding catheter at 3.5 mL/s, serving as a flush to clear the area of blood. The entire lesion was then imaged using an automatic pullback system moving at 20 mm/s.

2.4. OCT analysis

Lipid arcs were evaluated as the largest arc in a signal-pool region, with diffuse borders in the target plaques on the cross-sectional OCT image. Fibrous-cap thickness was defined as the minimum thickness of the signal-rich layer overlying the lipid-rich plaque. Lipid length was defined as the longitudinal length of the lipid-rich plaque (lipid arc ≥90°). Macrophage accumulation was identified as a high-intensity band or bright spots, which exceed the intensity of intra-tissue speckle noise, with high backscattering within the fibrous-cap, as previously reported [13]. Intimal microvessel was defined as a black hole or a tubular structure within a target plaque [11,13]. For each individual target plaque, the thinnest fibrous-cap thickness measurement obtained from three imaging locations was used for analysis (Fig. 1). At the time of follow-up, the plaques were identified based on the distance from the landmarks such as major branches, calcification and stent edge. Interobserver and intraobserver variabilities were assessed by the evaluation of all images by two independent readers who were blinded to the clinical presentations and the time point of image acquisition and by the same reader at two different times to compute an average value, respectively.

2.5. Clinical follow-up

Clinical events were monitored for at least 18 months after the index PCI. Death, MI, clinically driven revascularization for in-stent restenosis (defined as a repeat PCI or coronary artery bypass graft at the site of the implanted stent) were evaluated [17]. Clinically driven target plaque revascularization was defined as PCI or coronary artery bypass graft to the target TCFA lesion. Clinically driven non-target plaque revascularization was defined as repeat PCI or coronary artery bypass graft to a non-target TCFA lesion.

2.6. Statistical analysis

All statistical analyses were performed using Medcalc (version 12.7; Medcalc Software, Mariakerke, Belgium). Continuous variables are presented as means ± SD. Differences between the continuous parameters in the 2 groups were calculated using a Mann–Whitney *U*-test. Categorical variables are presented as frequency counts. Between group comparisons of categorical variables were performed using Fisher's exact test. Values were considered statistically significant at $p < 0.05$.

3. Results

3.1. Study population

Between April 2010 and October 2011, 341 patients underwent PCI at Kobe University Hospital; 117 patients had LDL levels >100 mg/dL and had not received lipid-lowering therapy. Of these 117 individuals, 22 patients were excluded from this study because of participation in other studies. A further 29 patients were excluded due to their inability to tolerate OCT examination or statin administration due to known hypersensitivity to contrast or statins ($n = 3$), end-stage renal failure ($n = 8$), severe heart failure ($n = 5$),