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Original article

A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins

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ABSTRACT

Background: There is a residual risk of coronary heart disease (CHD) despite intensive statin therapy for secondary prevention. The aim of this study was to investigate whether coronary plaque regression and stabilization are reinforced by the addition of eicosapentaenoic acid (EPA) to high-dose pitavastatin (PTV).

Methods: We enrolled 193 CHD patients who underwent percutaneous coronary intervention (PCI) in six hospitals. Patients were randomly allocated to the PTV group (PTV 4 mg/day, $n = 96$) or PTV/EPA group (PTV 4 mg/day and EPA 1800 mg/day, $n = 97$), and prospectively followed for 6–8 months. Coronary plaque volume and composition in nonstenting lesions were analyzed by integrated backscatter intravascular ultrasound (IB-IVUS).

Results: The PTV/EPA group showed a greater reduction in total atheroma volume compared to PTV group. IB-IVUS analyses revealed that lipid volume was significantly decreased during follow-up period in only PTV/EPA group. The efficacy of additional EPA therapy on lipid volume reduction was significantly higher in stable angina pectoris (SAP) patients compared to acute coronary syndrome patients. EPA/AA ratio was significantly improved in PTV/EPA group compared to PTV group. There was no significant difference in the incidence of major adverse cardiovascular events and side effects.

Conclusions: Combination EPA/PTV therapy significantly reduced coronary plaque volume compared to PTV therapy alone. Plaque stabilization was also reinforced by EPA/PTV therapy in particular SAP patients. The addition of EPA is a promising option to reduce residual CHD risk under intensive statin therapy.

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[1] For a complete list of the members of the CHERRY study, please see the supplemental material.

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Introduction

Many large-scale clinical trials have shown that statin therapy can prevent primary and secondary ischemic cardiovascular events [1]. Intravascular ultrasound (IVUS) studies have revealed that high-intensity statin treatment leads to coronary artery plaque regression and stabilization [2–4]. According to recent guidelines [5], high-intensity statin therapy without a specific low-density lipoprotein cholesterol (LDL-C) goal is recommended in secondary prevention. In fact, despite achieving LDL-C ≤70 mg/dL, >20% of patients demonstrate substantial disease progression [6]. Reducing residual risk is an unmet medical need for secondary prevention with high-intensity statin therapy.

Low serum long-chain n-3 polyunsaturated fatty acid (PUFA) levels are associated with coronary and carotid atherosclerosis progression [7,8]. Epidemiological and clinical studies showed that long-term intake of long-chain n-3 PUFAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can reduce morbidity and mortality due to coronary heart disease (CHD) [9,10]. In the JELIS trial [11], the addition of EPA to statin therapy was effective in primary and secondary CHD prevention. However, it remains to be determined whether the addition of EPA therapy can further prevent coronary atherosclerosis in CHD patients receiving high intensity statin therapy.

IVUS-based evaluation of coronary atherosclerosis progression-regression is reportedly a feasible surrogate endpoint to predict future cardiovascular events [12,13]. In the present study, we used integrated backscatter IVUS (IB-IVUS) to investigate whether coronary plaque regression and stabilization are reinforced by the addition of EPA to high-dose pitavastatin (PTV) therapy.

Methods

Study design

The CHERRY (combination therapy of eicosapentaenoic acid and pitavastatin for coronary plaque regression evaluated by integrated backscatter intravascular ultrasonography) study was a prospective, randomized, non-blinded, parallel, multicenter study to investigate the effect of adding EPA to high-dose PTV on coronary plaque analyzed by IB-IVUS. A detailed study protocol was published previously [14]. All procedures were performed in accordance with the Helsinki declaration. This study was approved by each institutional ethics committee, and written informed consent was obtained from each patient. This study was registered at University Hospital Medical Information Network (UMIN ID: 000002815).

The primary endpoint was the change in coronary plaque tissue characteristics as evaluated by IB-IVUS. The secondary endpoints included: (1) plaque volume; (2) the changes in total cholesterol (TC), LDL-C, triglyceride, high-density lipoprotein-cholesterol (HDL-C), malonyldialdehyde LDL (MDA-LDL), remnant-like particle-cholesterol (RLP-C), lipoprotein (a), and apolipoproteins; (3) EPA/arachidonic acid (AA) levels; (4) high-sensitivity C-reactive protein (hs-CRP); and (5) the incidence of major adverse cardiovascular events (MACE) defined as cardiac death, nonfatal myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting. Major bleeding was classified according to definition of International Society on Thrombosis and Haemostasis [15].

Patient enrollment and randomization

Patients with stable angina pectoris (SAP) and acute coronary syndrome (ACS) who satisfied the previously described inclusion and exclusion criteria were selected after successful PCI under IVUS guidance [14]. Briefly, patients who gave written consent after being provided with the details of clinical trial participation were included. Patients with familial hypercholesterolemia, hepatic dysfunction, or renal dysfunction (serum creatinine ≥2.0 mg/dL) were excluded. Patients were randomized for PTV therapy (4 mg/day) and PTV/EPA therapy (PTV 4 mg/day and EPA 1800 mg/day) by controlling for their diagnosis and the presence of diabetes mellitus. All patients received aspirin (100–200 mg/day) and clopidogrel (75 mg/day) for at least 6 months after PCI. The IB-IVUS examination was performed at baseline and the follow-up visit (6–8 months after PCI).

Laboratory assessment

Blood examinations were performed at baseline and follow-up at 6–8 months. Serum lipids, RLP-C, apolipoproteins, and hs-CRP were measured using routine laboratory methods. MDA-LDL and fatty acid fractions were measured at SRL Co., Ltd. (Tokyo, Japan).

IVUS examination

We performed grayscale and IB-IVUS examinations with a 40-MHz, 5-Fr IVUS imaging catheter (ViewIT™, Terumo, Tokyo, Japan) at baseline and follow-up. IVUS images were captured for as long as possible at a speed of 0.5 mm/s using a motorized pull-back system after intracoronary injection of isosorbide dinitrate.

IVUS analysis

IVUS and coronary angiographic images were analyzed at the core laboratory by experienced investigators using an IVUS imaging system (VISIWAVE or VISIATRAS, Terumo). Baseline and follow-up images were reviewed, and target segments were selected. One target segment was determined at a non-PCI site (>5 mm proximal or distal to the stenting site) with a reproducible index side branch on the PCI vessel. Grayscale IVUS analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement, and Reporting of Intravascular Ultrasound Studies [16]. Plaque analysis was performed in the target segment at 1-mm axial intervals. The external elastic membrane (EEM) cross-section area (CSA), lumen CSA, and plaque plus media CSA were manually measured in each slice. Plaque volume was calculated as the sum of plaque plus media in each CSA according to Simpson's rule. IB data for each tissue component were calculated as average power levels using a fast Fourier transform, measured in decibels, of the frequency component of backscattered signals from a small volume of tissue. We applied the manufacturer's default setting based on previous data [17]. Plaque components are classified into four color-coded images by IB scores measuring backscattered signals from the tissue: blue (lipid), green (fibrosis), yellow (dense fibrosis), and red (calcification) [18]. Volumetric IB-IVUS analysis was performed to calculate lipid volume, fibrosis volume, dense fibrosis volume, and calcification volume from the sum of lipid, fibrosis, dense fibrosis, and calcification in each CSA.

Percent atheroma volume (PAV) was calculated as follows:

$$\mathrm{PAV} = \frac{\sum(\mathrm{EEM} - \mathrm{Lumen\ area})}{\sum \mathrm{EEM\ area}} \times 100$$

Normalized total atheroma volume (TAV) was calculated as follows:

$$\mathrm{Normalized\ TAV} = \frac{\sum(\mathrm{EEM\ area} - \mathrm{Lumen\ area}) \times \mathrm{median\ no.\ of\ analyzed\ frames\ in\ the\ populations}}{\mathrm{no.\ of\ analyzed\ frames\ in\ each\ individual}}$$

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