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ORIGINAL ARTICLE

Effects of Combination of Ezetimibe and Rosuvastatin on Coronary Artery Plaque in Patients with Coronary Heart Disease

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Background In approximately 80% of cardiovascular disease-related deaths, patients suffer from coronary atherosclerotic heart disease. Ezetimibe is the first intestinal cholesterol absorption inhibitor. Its combination with statins for treating coronary atherosclerotic heart disease has attracted attention worldwide.

Methods The study group comprised 106 patients with coronary atherosclerotic heart disease and hyperlipidaemia. Each was randomly assigned to one of two groups: (1) Ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night) (n = 55) or (2) Rosuvastatin alone (10 mg, once a night) (n = 51). The primary endpoint was new or recurrent myocardial infarction, unstable angina pectoris, cardiac death, and stroke. Blood lipid, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) levels were measured before treatment and at one, six and 12 months after treatment. Coronary plaque size and compositional changes were determined using intravascular ultrasonography.

Results The combination of ezetimibe plus rosuvastatin decreased total cholesterol, low-density lipoprotein cholesterol, hsCRP, IL-6, and MMP-9 levels at six and 12 months after treatment. Statistical significance was detected between two groups. At 12 months, the plaque burden, plaque cross-sectional area, and percentage of necrotic plaque composition were significantly lower in the combination group than in rosuvastatin alone group ($P < 0.05$). And compared with rosuvastatin alone group, the primary endpoint decreased more effectively in combination group.

Conclusions The combination of ezetimibe and rosuvastatin apparently diminishes lipid levels and plaque burden and improves plaque stability, which may be associated with the potent inhibitory effects of ezetimibe and rosuvastatin on inflammatory cytokines.

Keywords Ezetimibe • Rosuvastatin • Coronary artery plaque • High-sensitivity C-reactive protein • Interleukin-6 • Matrix metalloproteinase-9

Introduction

In approximately 80% of cardiovascular disease-related death, patients suffer from coronary atherosclerotic heart disease [1]. Atherosclerosis is a complicated chronic inflammatory process whose primary essence includes an excessive inflammatory response and lipid accumulation [2]. At present, there are three main approaches to treating coronary atherosclerotic heart disease: drug therapy, percutaneous coronary intervention (PCI), and coronary artery bypass

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grafting. Drug therapy is a basis for all coronary heart disease patients. And it is the first choice for patients with borderline lesions, patients with severe coronary artery stenosis who cannot or are unwilling to undergo intervention, and/or coronary artery bypass grafting. Statins are effective medicine. Statins can effectively stabilise or reverse plaque, improve prognosis, and reduce mortality and morbidity by lowering blood lipid levels and inhibiting the inflammatory response within the already present atherosclerotic plaque [3]. So, in clinic statins are used to lower lipid levels and stabilise plaque for patients with coronary atherosclerotic heart disease. Some patients, however, react badly to the strongest statins even in the maximum doses. In those cases, it is necessary to combine statins with other kinds of lipid-lowering drugs. Ezetimibe is a newly developed lipid-lowering drug that can inhibit intestinal absorption of cholesterol. Its combination with statins for treating coronary atherosclerotic heart disease has attracted attention worldwide.

In this study, patients with borderline lesions and (or) severe coronary atherosclerotic heart disease combined with hyperlipidaemia, who cannot or are unwilling to undergo stenting or coronary artery bypass grafting, were administered a combination of ezetimibe and rosuvastatin or rosuvastatin alone. Intravascular ultrasonography (IVUS) and virtual histology were used to determine the coronary plaque size and compositional changes before and after treatment. This study observed the effects of potent lipid-lowering therapy on coronary lesions and inflammatory factors and analysed the possible mechanisms.

Methods

Subjects

All of the subjects in the study were inpatients at the Department of Cardiology, First Affiliated Hospital, Zhengzhou University, China, from January 2011 to January 2014. Inclusion criteria were that coronary angiography had revealed one or more atherosclerotic lesions near the middle of the coronary arteries; total cholesterol level was $\geq$ 5.2 mmol/L; and (or) low-density lipoprotein (LDL)-cholesterol level was $\geq$ 3.6 mmol/L. The atherosclerotic lesions were borderline lesions and (or) severe coronary atherosclerotic lesions. Borderline lesion was 40-70% stenosis demonstrated by quantitative coronary angiography. Severe lesion was more than 75% stenosis demonstrated by quantitative coronary angiography. Exclusion criteria were (1) contraindications for the intervention; (2) statin use is contraindicated, such as the patient has active hepatitis; (3) high (> two-fold normal) transaminase levels. The patients were randomly divided into two groups: (1) Ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night) (n = 55), paying attention to changes in lifestyle; and (2) Rosuvastatin alone (10 mg, once a night) (n = 51), paying attention to changes in lifestyle. The therapies administered were identical in the two groups. The primary endpoint was new or recurrence myocardial infarction, unstable angina pectoris, cardiac death, stroke. Blood lipid levels, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) were measured before treatment and at one, six, and 12 months after treatment. Coronary angiography and IVUS were conducted again at 12 months after treatment.

Ethics Approval of the Study Protocol

All experimental procedures were approved by the Clinical Trial Ethics Committee of Zhengzhou University (Zhengzhou, China). All patients signed informed consent forms for the interventional examination and treatment (including IVUS) and stated that their participation was voluntary.

Coronary Angiography

Conventional angiography was performed through the radial artery pathway. In case of failure, the right femoral artery was selected. Two experienced interventional cardiologists quantitatively analysed the extent of the coronary artery lesion. Blood vessels more than 2.5 mm in diameter were further examined.

Blood Analysis

All blood samples were obtained after an overnight fast. Serum levels of TC, TG, HDL-C, and LDL-C were measured by standard enzymatic methods in the laboratory of our hospital. High-sensitivity C-reactive protein was measured by immunoturbidimetric assay kit. Interleukin-6 and MMP-9 were measured by ELISA assay kit.

Intravascular Ultrasonography

After coronary angiography, IVUS was performed as follows. The probe (phased array, 20 MHz, 3.2 F) (Eagle Eye; Volcano Corp., San Diego, CA, USA) was placed in the distal end of a stenotic lesion with a coronary guidewire and then moved to the proximal end at a speed of 0.5 mm/s. Grayscale IVUS images and virtual histology–IVUS images (IVUS mainframe: Volcano S5; Volcano Corp.) were continuously recorded on a carved disk, and then analysed by two experienced physicians. Using grayscale IVUS images, some indexes were measured: External elastic membrane area (EEM), minimum lumen area (MLA), plaque cross-sectional area (EEM–MLA), and plaque burden—i.e., area stenosis rate (MLA/EEM $\times$ 100%). Ten consecutive images of most stenotic regions were selected for the above measurement, and the average value was calculated. Using virtual histology–IVUS images, plaque components were categorised into four colours. White represented calcified tissue, red represented the necrotic core, light green represented fat and fibrous tissue, and dark green represented fibrous tissue, which is recorded as the percentage of various components to the total area of the plaque.

Statistical Analysis

All data were analysed using SPSS 13.0 software (SPSS, Chicago, IL, USA). Numerical data were expressed as a rate. Measurement data were expressed as the mean $\pm$ SD. The means of the two groups were compared using an independent sample t-test. The means in a group before and after