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Original article

Effect of olmesartan on the levels of circulating endothelial progenitor cell after drug-eluting stent implantation in patients receiving statin therapy

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ABSTRACT

Background: The endothelial progenitor cell (EPC) plays an important role in repairing vascular injury. Statins and angiotensin II receptor blockers increase the level of circulating EPCs. However, it is unknown whether the angiotensin II receptor blocker olmesartan synergistically acts with statins to increase the levels of circulating EPCs. Moreover, the association between the levels of circulating EPCs and endothelial dysfunction after implantation of drug-eluting stents (DESs) has not been evaluated.
Methods: Nine patients with stable coronary artery disease underwent percutaneous coronary intervention (PCI) and received DES implantation. All patients received olmesartan in addition to statin therapy after PCI. The dose of olmesartan was based on the physician's discretion as per the patients' blood pressure. The levels of circulating EPCs were analyzed at baseline, post-PCI, and 1, 2, 3, and 8 months after PCI. Coronary angiography and the acetylcholine provocation test were performed on all patients at 8 months.
Results: Although the angiotensin II level significantly changed, the levels of circulating EPCs did not change during 8 months of olmesartan treatment (3.1 ± 0.6 cells/ml, 2.5 ± 0.8 cells/ml, 2.0 ± 0.6 cells/ml, 2.9 ± 0.9 cells/ml, 3.0 ± 0.4 cells/ml, 3.4 ± 0.8 cells/ml, $p = 0.64$). The patients were subsequently divided into two groups based on whether the level of circulating EPCs was less or greater than 4 cells/ml at 8 months. There were no significant differences in the mean vessel diameter of each segment (proximal, proximal edge, distal edge, and distal) after the acetylcholine provocation test between the two groups.
Conclusions: Low-to-moderate doses of olmesartan might not increase the level of circulating EPCs in patients receiving statin therapy. There might be no association between the levels of circulating EPCs and the degree of coronary vasospasm in the acetylcholine provocation test 8 months after DES implantation.

Introduction

Circulating endothelial progenitor cells (EPCs) play an important role in repairing vascular injury through rapid endothelial regeneration [1,2]. EPCs are a key component of vascular healing after percutaneous coronary intervention (PCI) [3]. Nonetheless, cardiovascular risk factors are associated with reduced number of circulating EPCs [4–7]. Statins and certain antihypertensive drugs, such as angiotensin II receptor blockers (ARBs), increase the levels of circulating EPCs [4,8–11]. Atorvastatin increases the level of circulating EPCs by a factor of 3 in patients with stable coronary artery disease [8]. Olmesartan also increases the level by a factor of 2 in patients with type II diabetes [11]. However, to the best of our knowledge, no data are available on whether these drugs act synergistically. Therefore, we evaluated the effect of olmesartan on the level of circulating EPCs after PCI in patients receiving statin therapy. Because endothelial dysfunction can occur following the implantation of drug-eluting stents (DESs), we investigated whether this adverse event is associated with the number of circulating EPCs.

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Methods

Patients and study protocol

Nine patients with stable coronary artery disease underwent PCI, and DES was implanted in the lesion. Angiotensin-converting enzyme inhibitors and ARBs were not prescribed before PCI; however, statins were prescribed at least 3 months before the procedure for all patients [atorvastatin 10 mg/day ($n = 3$), rosuvastatin 2.5 mg/day ($n = 2$), rosuvastatin 5 mg/day, rosuvastatin 10 mg/day, pitavastatin 1 mg/day, and pitavastatin 2 mg/day ($n = 1$)]. Olmesartan was started after PCI, and the dose was based on the physician's discretion according to the patient's blood pressure. We determined the number of circulating EPCs (baseline, post-PCI, and after 1, 2, 3, and 8 months) and the levels of angiotensin II (baseline, 1, 3, and 8 months), inteleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), monocyte chemotactic protein-1 (MCP-1), and P-selectin (baseline, post PCI, and after 1, 3, and 8 months). Follow-up coronary angiography and the acetylcholine provocation test were performed at 8 months for all patients. The primary endpoint of the present study was the level of circulating EPCs during 8 months. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or use of an antihypertensive drug. Dyslipidemia was defined as low-density lipoprotein cholesterol >100 mg/dl, high-density lipoprotein cholesterol ≤50 mg/dl, triglycerides ≥150 mg/dl, or medication use. This study was reviewed and approved by the local Ethics Review Committee, and written informed consent was obtained from all patients.

Interventional protocol and quantitative coronary analysis

All interventions were performed using standard techniques. The type of DES was chosen according to the physician's discretion. All patients were advised to continue treatment with dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) for 12 months after PCI and lifelong daily use of aspirin. The acetylcholine provocation test was performed along with follow-up angiography after 8 months. After baseline angiography, incremental doses of acetylcholine (50 and 100 μg/20 s into the left coronary artery and 25 and 50 μg/20 s into the right coronary artery) were infused directly through the catheter. After an additional 5 min, intracoronary isosorbide dinitrate (5 mg/10 s) was infused into the right and left coronary arteries. Qualitative and quantitative coronary angiography was evaluated at an independent angiographic core laboratory (Cardiocore, Tokyo, Japan) using a Coronary Angiography Analyses System (Medis QAngio XA 7.1, Leiden, The Netherlands). Baseline, post-procedure, and follow-up angiograms were obtained from all patients. The target segment was defined as the entire segment involving the implanted stent and the 5-mm proximal and distal edges adjacent to the stent. In the acetylcholine provocation test, a reference vessel not related to the stent lesion was analyzed (5–15 mm proximal and distal to the stent edges). We divided the enrolled patients into two groups based on the level of circulating EPCs (4 cells/ml) and compared the results of the acetylcholine provocation test between the two groups.

Level of circulating EPCs

A 20-ml sample of peripheral blood was obtained from each patient, and the number of circulating EPCs was determined within 24 h (SRL, Tokyo, Japan) using a fluorescence-activated cell sorter (FACScan, Becton Dickinson, Franklin Lakes, NJ, USA). EPCs were identified by the presence of CD34, CD45, CD133, and CD133 antigens (Fig. 1).

Statistics

Continuous variables are expressed as mean ± standard deviation (SD) and compared using Student's t test. The values for all blood samples for all time points were compared using repeated measure analysis of variance (ANOVA). All statistical tests were two-tailed. Statistical significance was defined as $p = 0.05$.

Results

Baseline characteristics and outcomes

Nine patients were enrolled in this study. Table 1 presents their baseline characteristics. Their mean age was 70 years. All patients had dyslipidemia and received statin therapy at least 3 months before the procedure. Patients received 40 mg ($n = 3$) or 20 mg doses ($n = 6$) of olmesartan during follow-up. Lesion and procedural characteristics are presented in Table 2. Sirolimus-eluting and

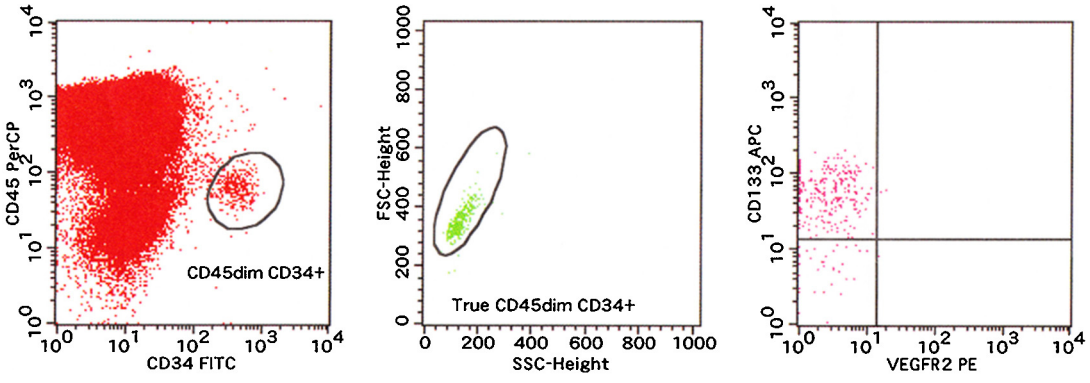

Fig. 1. The number of endothelial progenitor cells was determined using flow cytometry to detect CD34, CD45, CD133, and VEGFR2 antigens.