Carotid Plaque Characteristics on Magnetic Resonance Plaque Imaging Following Long-term Cilostazol Therapy

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Background: Cilostazol is an antiplatelet agent that can induce the regression of atherosclerosis. However, its long-term effects on plaque involution of the cervical carotid arteries remain unknown. Thus, we aimed to evaluate the effect of long-term cilostazol administration on carotid plaques using quantitative magnetic resonance (MR) plaque imaging. *Methods:* Sixteen consecutive patients with carotid stenosis were examined using T1-weighted MR plaque imaging at baseline, 6 months, and 12 months after initiation of 200 mg per day of cilostazol. We calculated the contrast ratio of the carotid plaque against the sternocleidomastoid muscle and percent areas of the intraplaque fibrous tissue, lipid/necrosis, and hemorrhage components using automated software. We also measured the volume and echogenicity of the plaques using 3-dimensional ultrasonography. *Results:* The contrast ratio of the carotid plaque significantly decreased during the cilostazol administration (median 1.07, 1.04, and 1.00 at baseline, 6 months, and 12 months, respectively; $P = .03$). Furthermore, the area of the fibrous components significantly increased (73.9%, 80.3%, and 85.7%, respectively; $P = .03$) and that of the lipid/necrotic components significantly decreased (25.2%, 19.2%, and 14.3%, respectively; $P = .04$). There were no substantial changes in plaque volume or echogenicity on ultrasonography. *Conclusions:* Signal alterations on MR plaque imaging indicated the increase of fibrous components and the decrease of lipid/necrotic components in the carotid plaque during the cilostazol therapy. **Key Words:** Atherosclerotic plaque—carotid stenosis—cilostazol—magnetic resonance imaging—plaque imaging.

Introduction

Atherosclerotic plaque of the cervical carotid artery can cause ischemic stroke by inducing hemodynamic ischemia or artery-to-artery embolism. Plaque volume as well as intraplaque vulnerable components, that is, lipid/necrotic and hemorrhagic components, are considered substantial risks for stroke events and can be a target of surgical procedures such as carotid endarterectomy (CEA) and carotid arterial stenting (CAS). In patients who are not candidates for CEA or CAS, medical treatment that reduces plaque volume or vulnerable components may effectively prevent stroke events. Statins are widely used for this purpose and are reported to reduce low-density lipoprotein-cholesterol and carotid intima-media thickness (IMT).[1] Cilostazol, an antiplatelet agent

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that inhibits phosphodiesterase III in platelets and the vascular endothelium,[2,3] can also be administered for the same purpose; it may induce the regression of atherosclerotic changes,[4-6] presumably due to its pleiotropic effects of improved lipid metabolism, suppressed cytokine production, and restored arterial endothelial function.[7-10] Previous studies have demonstrated that cilostazol administration over a relatively short period can reduce IMT, observed on ultrasonography (US), and vulnerable components, observed on magnetic resonance imaging (MRI).[11] However, the effects of long-term cilostazol administration on carotid plaque characteristics are unknown. Therefore, this study aimed at examining carotid plaque changes via quantitative magnetic resonance (MR) plaque imaging after 6 and 12 months of cilostazol administration.

Materials and Methods

Patients

Between November 2009 and February 2012, 16 consecutive patients (12 men and 4 women; age range, 56-79 years; median, 67 years) with unilateral or bilateral cervical carotid stenosis detected by cervical US were enrolled. The patients were identical to those in our previous preliminary study[11] and fulfilled the following criteria: noncandidate for CEA or CAS, no previous administration of cilostazol, and no changes in medical treatment for at least the last 6 months. Of 18 internal carotid arteries with 6%-77% (median, 45%) stenosis according to the European Carotid Surgery Trial method, 11 lesions were asymptomatic and 7 were symptomatic. The patients' demographics included hypertension in 13 patients, hyperlipidemia in 11 patients, and diabetes mellitus in 7 patients as well as administration of statin drugs in 9 patients, angiotensin-2 receptor blocker in 9 patients, and insulin in 3 patients.

The patients were administered 100 mg cilostazol (Otsuka Pharmaceutical Corporation, Tokyo, Japan) orally twice a day and underwent MR plaque imaging and 3-dimensional (3D) US (3D-US) at baseline, just before initiation of cilostazol administration (within 1 week), and again 6 months (median, 187 days; range, 149-212 days) and 12 months (median, 379 days; range, 352-389 days) after the initiation. We carried out all examinations after obtaining approval from the institutional review board and written informed consent from each patient.

Imaging Protocol

Axial T1-weighted images of the carotid bifurcation were obtained using a 1.5-T MRI system (Echelon Vega; Hitachi Medical Corporation, Tokyo, Japan) with an 8-channel neurovascular coil. The pulse sequence parameters were as follows: spin echo (SE); repetition time, 500 ms; echo time, 12 ms; field of view, 18 cm; matrix size, 256 × 256 (pixel size, .35 × .35 mm^2 after zero-fill interpolation); slice thickness, 4.0 mm with interslice gaps of 1 mm; number of slices, 9; number of excitations, 2; fat suppression, chemical shift-selective saturation; and acquisition time, 6 minutes 46 seconds. As a motion correction technique, we used a radial scan with self-navigation adopted from the periodically rotated overlapping parallel lines with enhanced reconstruction method,[11] as reported previously.[12] As a black-blood method, presaturation pulses at the superior and inferior sides of the section locations were used. The direction of the sections was parallel to the short axis of the carotid bifurcation on the sagittal two-dimensional (2D) phase-contrast MR angiography images. The position and angulation of the sections at the follow-up scans were carefully set to be identical to those at the baseline scan.

The patients underwent 3D B-mode and color Doppler examination of the affected carotid bifurcations within 1 week before/after MR examinations at the baseline and follow-up periods by the operator who had extensive experience (K.O.) using a 3D-US scanner (VOLUSON 730 Expert; GE Healthcare, Milwaukee, WI) with a 5-12 MHz 3D/4D probe.

Data Processing and Statistical Analysis

We used a software package for plaque analyses (Plaque Viewer; Hitachi Medical Corporation, Tokyo, Japan). One of the authors (M.Y.), who was blinded to the patient information and scan time points, manually traced the plaques and adjacent sternocleidomastoid muscles on the image in which the plaque was the largest using a polygon cursor. The contrast ratio (CR) of the plaque against the muscle and the percent area of the intraplaque components (ie, fibrous tissue, lipid/necrosis, and hemorrhage components) were automatically calculated. The cutoff values of the CRs (fibrous tissue <1.17; lipid/necrosis, 1.17-1.55; hemorrhage >1.55) were adopted from a recent histopathologic correlation study.[13] These measurements were performed 3 times, and the values were then averaged.

To evaluate the US images, one of the authors (K.O.) measured the plaque volume by manually tracing the plaque boundaries on contiguous reformatted images using the software on the scanner console in a blinded fashion. In addition, the same operator generated axial reformatted images corresponding to the MR images, converted these to JPEG format, and measured the gray scale median (GSM) values of the plaques by manually tracing using a polygon cursor and a graphic software package (Photoshop CS4; Adobe Systems, San Jose, CA) in a blinded fashion after normalizing the gray scale according to criteria reported previously (0 for the lumen and 195 for the adventitia).[14,15] All measurements on the US images were performed 3 times, and the values were averaged.