Lipid Lowering by Simvastatin Induces Regression of Human Atherosclerotic Lesions
Two Years’ Follow-Up by High-Resolution Noninvasive Magnetic Resonance Imaging

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Background—Statins are widely used to treat hypercholesterolemia and atherosclerotic disease. Noninvasive MRI allows serial monitoring of atherosclerotic plaque size changes. Our aim was to investigate the effects of lipid lowering with simvastatin on atherosclerotic lesions.

Methods and Results—A total of 44 aortic and 32 carotid artery plaques were detected in 21 asymptomatic hypercholesterolemic patients at baseline. The effects of statin on these atherosclerotic lesions were evaluated as changes versus baseline in lumen area (LA), vessel wall thickness (VWT), and vessel wall area (VWA) by MRI. Maximal reduction of plasma total and LDL cholesterol by simvastatin (23% and 38% respectively; \( P < 0.01 \) versus baseline) was achieved after \( \approx 6 \) weeks of therapy and maintained thereafter throughout the study. Significant \( (P < 0.01) \) reductions in maximal VWT and VWA at 12 months (10% and 11% for aortic and 8% and 11% for carotid plaques, respectively), without changes in LA, have been reported. Further decreases in VWT and VWA ranging from 12% to 20% were observed at 18 and 24 months. A slight but significant increase (ranging from 4% to 6%) in LA was seen in both carotid and aortic lesions at these later time points.

Conclusion—The present study demonstrates that maintained lipid-lowering therapy with simvastatin is associated with significant regression of established atherosclerotic lesions in humans. Our observations indicate that lipid-lowering therapy is associated with sustained vascular remodeling and emphasize the need for longer-term treatment.

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Key Words: lipids ■ atherosclerosis ■ plaque ■ magnetic resonance imaging

Lipid-lowering therapy with statins can significantly decrease cardiovascular morbidity and mortality when used in primary and secondary prevention.\(^1\) Statins seem to exert their benefits through inhibition of de novo cholesterol synthesis, resulting in significant reductions of total and LDL cholesterol plasma levels. Whether this is the only mechanism of action responsible for the observed benefits remains controversial. Indeed, additional non–lipid-dependent, or “pleiotropic,” effects have been postulated.\(^1\) Experimental\(^2\) and clinical\(^3,4\) evidence supports the notion that statin therapy stabilizes high-risk (vulnerable) lesions by reducing their lipid content and inflammation, thus increasing fibromuscular/lipid tissue ratio.

MRI has emerged as the most promising noninvasive technique for longitudinal in vivo study of large atherosclerotic arteries. Its usefulness for the in vivo study of plaque progression, stabilization, and even regression has been demonstrated in several animal models.\(^4,5,6\)

We have reported that, despite early hypolipidemic effect, at least 1 year of treatment was needed to detect significant changes in plaque size.\(^9\) In fact, no changes were seen at 6 months, whereas at 12 months, significant reductions in vessel wall thickness and vessel wall area, without changes in lumen area, were noted. We postulated that statins reduce atherosclerotic burden without affecting the lumen size. These preliminary results were recently confirmed in a cross-sectional case-control study reporting reductions in plaque size and lipid core in patients receiving an aggressive lipid-altering regimen for 10 years.\(^8\) More importantly, prospective angiographic studies demonstrated that simvastatin abolished progression of stenotic coronary lesions\(^10\) and that...
The combination of simvastatin and niacin has the potential to reduce the degree of stenosis.11

Our objective was to investigate prospectively the long-term effects of lipid lowering by simvastatin on human atherosclerotic lesions. The study design allowed each subject to serve as his/her own control, and hence, to study progression or regression of atherosclerotic lesions with MRI.

Methods

Study Design and Patients

Study population and design have been previously reported.9 In brief, the inclusion criteria were based on asymptomatic and untreated dyslipidemia (LDL cholesterol >130 mg/dL) and the existence of atherosclerotic plaques (thoracic aortic plaques ≥ 4.0 mm or carotid artery plaques ≥ 2.0 mm thick) documented by ultrasound and/or MRI. A total of 44 aortic and 32 carotid artery plaques were detected in the 21 patients enrolled. The institutional review board approved the protocol.

Serial MRI studies of the thoracic aorta and carotid arteries were performed at baseline and every 6 months. The following were the baseline characteristics of the patients: sex, 12 male, 9 female; age, 63.5 ± 9 years; total cholesterol, 240 ± 73 mg/dL; LDL cholesterol, 159 ± 32 mg/dL; HDL cholesterol, 52 ± 16 mg/dL; and triglycerides, 164 ± 106 mg/dL.

MRI Protocol

Sequential MRI was performed on a 1.5T whole-body MRI system (Signa CV/i; GE Medical Systems; 40 mT/m) as previously reported.9 In brief, a customized 4-element (2 elements placed on either side of the neck) phased-array coil with head-holder (to reduce motion) was used for carotid imaging. A 4-element (2 anterior and 2 posterior) coil was used for aortic imaging. After localization with a fast-gradient echo sequence, all images were obtained with a double-inversion recovery (ie, black blood) fast-spin-echo sequence with ECG gating during free breathing (Figure 1). The total examination time for aortic and carotid imaging was 60 to 90 minutes.

A total of 25 to 30 transverse images centered at the carotid bifurcation were taken. For aortic lesions, 25 to 30 axial images, from the origin of the left subclavian artery to the level of the diaphragm, were obtained. For the aortic arch, 10 to 12 cross-sectional oblique images perpendicular to the vessel wall were acquired. The imaging parameters have been previously reported.9

The in-plane resolution was 780 x 780 μm for the aorta and 469 x 469 μm for the carotid artery.

Morphometric Analysis

Special attention was paid to matching as closely as possible the magnetic resonance (MR) images of the same patient at the different follow-up time points by the use of several anatomic landmarks (eg, carotid bifurcation, top of the aortic arch, origin of the coronaries, pulmonary artery bifurcation and pulmonary veins) (Figure 1, D and E). To minimize submillimeter errors in the matching of the images at different time points, at least 5 contiguous MR images per plaque were analyzed and the average used for statistical analysis. The accuracy of the measurement of vascular dimensions was previously reported.9 We calculated that changes in plaque size of ≥ 5% for aortic and ≥ 7% for carotid lesions can be accurately measured by MRI.

The lumen area (LA); total vascular area (TVA); minimal, maximal, and mean vessel wall thickness (VWT); and vessel wall area (VWA=TV A−LA) were calculated by computer-assisted morphometric analysis of cross-sectional MR images (Image Pro-Plus, Media Cybernetics). The investigator performing the measurements was blinded to the patient’s identity and time sequence of images.

Statistical Analysis

Data are presented as mean ± SEM. Statistical analysis was performed with ANOVA for repeated measures (post hoc Bonferroni) or Student’s t test (StatView 4.1, ABACUS Inc). A value of P<0.01 was considered significant.

Results

Effect on Plasma Lipid Levels

The effects of simvastatin administration on plasma lipid levels throughout the study period are presented in Figure 2. Simvastatin induced a significant reduction in total and LDL cholesterol levels, whereas HDL cholesterol levels increased slightly. The maximal hypolipidemic effect was achieved at 6 weeks of therapy and was maintained for the duration of the study.

Effect on Atherosclerotic Plaques

Significant reductions in VWA and VWT were observed at 12, 18, and 24 months after therapy initiation (Figure 3). The changes observed at 24 months were statistically significantly versus baseline (before treatment) and also when compared with the 12-month data. For aortic lesions, 13% and 16% decreases in VWA at 18 and 24 months, respectively, were observed. Similar reductions were observed for maximal
VWT, which decreased by 12% and 16% at 18 and 24 months, respectively. No changes were detected for minimal VWT, suggesting that the observed reductions in VWA are consequences of decreases in the thickest region of the lesions and are not due to homogeneous shrinkage of the arterial wall. Similar changes were detected in the carotid lesions: VWA decreased by 16% at 18 months and 18% at 24 months, and the maximal VWT decreased by 15% and 19% at 18 and 24 months, respectively.

More important is the observation that long-term lipid-lowering therapy may significantly affect the arterial lumen. Increases in lumen size were first detected at 18 months on treatment in both carotid and aortic arterial beds (Table). Aortic lumen increased by 5% and 6% at 18 and 24 months, respectively. Carotid artery lumen increased by 4% and 5% at 18 and 24 months, respectively.

Interestingly, TVA progressively decreased until 12 months of treatment for aortic lesions and 18 months for carotid lesions, and it remained unchanged thereafter. This observation may indicate that maximal vessel wall remodeling was achieved at ≈18 months of treatment (Figure 4).

**Discussion**

We are describing the beneficial effects of long-term, effective lipid lowering by simvastatin on previously established aortic and carotid atherosclerotic lesions. Our observations demonstrate that simvastatin may not only reduce the VWA (vascular atherosclerotic burden), but if treatment is maintained, also increase the arterial luminal area. The observation that a longer treatment period was required before effect on arterial lesions was detected is consistent with the outcome of large event-based studies. This observation emphasizes the need for sustained lowering of LDL cholesterol to favorably impact the progression of atherosclerotic disease. The earliest change was a regression in plaque size, illustrated by the reduction of the arterial wall area without affecting the luminal area. Longer follow-up indicated that regression of atherosclerotic lesions continues for at least 24 months and that progressive remodeling of the arterial wall produces a significant increase in luminal area. Our observations suggest that, at least in the early lesions studied here, plaque shrinkage and vascular remodeling may be achieved before reasonable effects on luminal dimensions. Significant increase in LA (ranging from 4% to 6%) was detected after 24 months. Even though previous studies with angiographic end points failed to demonstrate significant changes in lumen diameter, similar changes recently were seen in the common carotid artery of familial hypercholesterolemic patients when intima-media thickening was measured by high-resolution ultra-
sound. Interestingly, the feature of arterial remodeling, detected as a decrease in the total VWA, was not sustained after the first 18 months of treatment. These data confirm the original observation by Glagov et al that in the early stages of atherogenesis, lipid deposition is associated with a positive outer remodeling of the arterial wall, whereas at later stages, continuous lipid and cell accumulation start compromising the arterial lumen. Conversely, an effective lipid-lowering treatment may, by reducing the lipid content of the lesions, affect the remodeling of the vascular wall before significantly affecting the luminal area. The imaging capabilities of high-resolution MRI have greatly facilitated these observations.

The evidence accumulated in experimental studies during the past few decades indicates that atherogenesis initially involves the intima and is initiated by endothelial dysfunction with progression in the subendothelial space. Recently, several regression studies have been performed with lipid lowering in different animal models of atherosclerosis. These studies revealed that the drastic biological changes within the atherosclerotic plaque are mainly located in the areas of high macrophage content. Studies have also highlighted the important role of the media and adventitia in atherogenesis, in particular in the process of remodeling. Advances in imaging techniques, such as the use of ultrasmall superparamagnetic particles of iron oxide (taken up by macrophages and scavenged into the plaque) and MR molecular imaging (for the detection of metalloproteinases, apoptosis, and gene expression), may allow better characterization of the biological effects of statins.

The present study does not address the effect of statins on coronary atherosclerotic lesions. Recently, Brown et al confirmed that simvastatin and niacin taken together can stop the progression of luminal narrowing in patients with coronary artery disease. Whether statin treatment could induce regression of established coronary plaques is still debated. Clinical trials designed to prospectively analyze the effects of lipid-altering approaches on coronary plaques are needed.

In conclusion, our study demonstrates a progressive reduction of aortic and carotid plaque size during 2 years of treatment with simvastatin. Regardless of plaque location, the percent change in plaque area and thickness and lumen was similar for aortic and carotid plaques, confirming the systemic effect of treatment with simvastatin.

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