Arthritis Care & Research
Vol. 63, No. 6, June 2011, pp 875–883
DOI 10.1002/acr.20440

ORIGINAL ARTICLE

Effects of Rosuvastatin on Vascular Biomarkers and Carotid Atherosclerosis in Lupus: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. **To study the effect of rosuvastatin on vascular biomarkers and carotid intima-media thickness (IMT) in systemic lupus erythematosus (SLE).**

Methods. **SLE patients with inactive disease and subclinical atherosclerosis were randomized in a double-blinded manner to receive either rosuvastatin (10 mg/day) or matching placebo (half in each group were also randomly allocated low-dose aspirin). After 12 months, treatment was unblinded. Patients treated with rosuvastatin and aspirin were continued on the same medications for another 12 months. Plasma levels of homocysteine, high-sensitivity C-reactive protein (hsCRP), soluble vascular cell adhesion molecule 1, P-selectin, and thrombomodulin were measured at baseline, 6 months, and 12 months. Measurement of carotid IMT was repeated at 24 months.**

Results. **Seventy-two patients were studied (97% women, mean ± SD age 50.8 ± 9.7 years). Thirty-six patients were randomly assigned to each of the study arms (18 patients in each arm also received aspirin). Baseline clinical characteristics and medications were similar between the two groups. At 12 months, the mean low-density lipoprotein cholesterol (mean ± SD 2.62 ± 1.04 mmoles/liter to 1.69 ± 0.72 mmoles/liter; $P < 0.001$) and median hsCRP levels (1.26 mg/liter, interquartile range [IQR] 2.3 to 0.88 mg/liter, IQR 1.1; $P = 0.02$) decreased significantly in the rosuvastatin group. There was no significant change in homocysteine, and aspirin use did not influence the levels of the biomarkers studied. A subgroup analysis of patients with a Systemic Lupus Erythematosus Disease Activity Index score ≤2 revealed a significant decrease in hsCRP (1.20 mg/liter, IQR 2.3 to 0.92 mg/liter, IQR 1.1; $P = 0.04$) and thrombomodulin levels (0.76 ng/ml, IQR 1.2 to 0.67 ng/ml, IQR 1.0; $P = 0.001$) with rosuvastatin treatment. At 24 months, the IMT of the internal carotid arteries appeared to be decreased in patients treated with rosuvastatin, which was well tolerated.**

Conclusion. **In stable SLE patients, low-dose rosuvastatin leads to a significant reduction in hsCRP and thrombomodulin levels, which may possibly help to reduce cardiovascular risk.**

INTRODUCTION

Patients with systemic lupus erythematosus (SLE) are prone to accelerated atherosclerosis. In cross-sectional studies, approximately one-third of patients with SLE had evidence of subclinical atherosclerosis at the carotid or coronary arteries (1,2). A longitudinal study has also shown that carotid atherosclerosis progresses over time in 28% of patients (3). Therefore, preventing the progression of atherosclerosis is the key strategy to reduce the risk of arterial thrombosis in patients with SLE.

The hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have lipid-lowering and anti-inflammatory properties. Statins have proven benefits in the primary and secondary prevention of acute myocardial infarction (MI) and stroke (4–7). In recent trials of MI, subjects who achieved a target level of high-sensitivity C-reactive protein (hsCRP) of ≤2 mg/liter with statin treatment have a significant reduction in recurrence of MI or mortality, an effect independent of the achieved levels of low-density lipoprotein (LDL) cholesterol (8,9). This suggests that lowering of LDL cholesterol and hsCRP levels

ClinicalTrials.gov identifier: NCT00371501.

AstraZeneca provided the study drug samples and placebo tablets. The biomarker assay was supported by the research fund of Tuen Mun Hospital, Hong Kong.

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Submitted for publication September 15, 2010; accepted in revised form January 18, 2011.

are two independent effects of statins that lead to a reduction of vascular events.

Rosuvastatin is one of the many potent statins available in the market. In low-risk patients with subclinical carotid atherosclerosis, a randomized controlled trial showed that rosuvastatin (40 mg/day) significantly slows down progression of carotid intima-media thickness (IMT) after 2 years of treatment compared to placebo (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin) (10). Another placebo-controlled randomized controlled trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) demonstrated that in apparently healthy men and women, rosuvastatin (20 mg/day) treatment resulted in a significant reduction of vascular events after a median of 1.9 years (4). Cardiovascular protection was greatest when the LDL cholesterol level was reduced to <1.8 mmoles/liter and the hsCRP level was reduced to <2 mg/liter.

The objective of the current work was to study the effect of rosuvastatin treatment on hsCRP, homocysteine, biomarkers of endothelial activation/injury, and the change in carotid IMT in stable SLE patients with subclinical atherosclerosis.

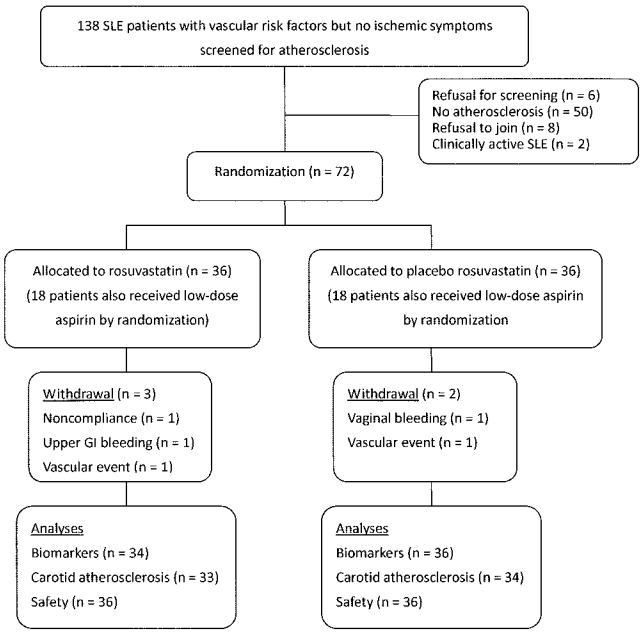

Figure 1. Patient enrollment and disposition. SLE = systemic lupus erythematosus; GI = gastrointestinal.

PATIENTS AND METHODS

Study objectives and population. Patients who fulfilled ≥4 American College of Rheumatology criteria for the classification of SLE (11) were invited to participate in this study. The inclusion criteria were: 1) age ≥18 years, 2) abnormal coronary calcification (Agatston score ≥1) by multidetector computed tomography (MDCT) scan or abnormal carotid IMT (≥0.8 mm [population mean + 2 SDs] at any site) by B-mode ultrasound, 3) absence of vascular ischemic symptoms (e.g., angina, transient ischemic attack, intermittent claudication), 4) absence of history of arterial thrombosis (e.g., coronary heart disease, stroke, peripheral vascular disease), 5) absence of clinical symptoms of active lupus and a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of ≤6, and 6) a signed written informed consent was able to be obtained. The exclusion criteria were: 1) age <18 years, 2) history of intolerance or allergy to the statins, 3) had ever received statins within 12 months of study entry, 4) symptoms of vascular ischemia, 5) history of arterial thromboembolism, 6) clinical symptoms of active lupus or SLEDAI score >6, and 7) pregnant or lactating women. The protocol of this study was approved by the Research and Ethics Committee of our hospital and registered in the US ClinicalTrials.gov web site.

The original objectives of the study were to look at the effect of rosuvastatin (supplied by AstraZeneca) on endothelial markers at 12 months and the progression of carotid atherosclerosis at 24 months, and the efficacy of low-dose aspirin in reducing the incidence of arterial thromboembolism at 5 years. However, the latter objective was later terminated because of the anticipated difficulty in maintaining patients on study medications for 5 years, issues of manpower, and supply of study medications. Finally, only the first 24-month phase of the study was completed.

Study protocol. Patients who consented for the study were randomized by block in a double-blinded manner into 4 groups: 1) rosuvastatin (10 mg/day) + aspirin (80 mg/day), 2) rosuvastatin (10 mg/day) + placebo aspirin (1 tablet/day), 3) placebo rosuvastatin (1 tablet/day) + aspirin (80 mg/day), or 4) placebo rosuvastatin (1 tablet/day) + placebo aspirin (1 tablet/day) for 12 months. After 12 months, treatment was unblinded and the rosuvastatin group of patients was continued on rosuvastatin (open-label extension, same dosage) for another 12 months. Patients treated with placebo rosuvastatin were continued to be followed without rosuvastatin. Those who received aspirin also continued aspirin for another 12 months. The rosuvastatin, aspirin, placebo rosuvastatin, and placebo aspirin tablets were managed by a designated pharmacist in our pharmacy department. Because the part of the study on the efficacy of aspirin in preventing arterial thrombosis was abolished, we analyzed and presented results with respect to two groups of patients who received rosuvastatin or placebo rosuvastatin.

During the study period, other medications were continued and flares of SLE during the study period were treated with the usual protocols, as judged by the attending physicians. Plasma levels of homocysteine, hsCRP, soluble vascular cell adhesion molecule 1 (VCAM-1), P-selectin, and thrombomodulin were measured at baseline, 6 months, and 12 months. IMT of the carotid arteries was measured at baseline and 24 months. SLEDAI scores

Table 1. Baseline clinical characteristics, vascular risk factors, and medications*

	Rosuvastatin arm (n = 36)	Placebo arm (n = 36)	All (n = 72)	*P*
Women, no. (%)	34 (94)	36 (100)	70 (97)	0.47
Age at entry, years	51.3 ± 10.4	50.3 ± 9.2	50.8 ± 9.7	0.66
Duration of SLE, years	12.4 ± 8.1	11.2 ± 5.9	11.8 ± 7.1	0.48
Carotid IMT, mm	0.68 ± 0.11	0.66 ± 0.15	0.67 ± 0.13	0.69
Agatston score	31.7 ± 72	30.2 ± 65	30.9 ± 68	0.93
SLEDAI score	1.4 ± 1.5	1.8 ± 2.0	1.6 ± 1.7	0.26
SLEDAI AUC, first 12 months	17.6 ± 20	22.7 ± 22	20.2 ± 21	0.31
SDI score	1.4 ± 1.6	1.2 ± 1.3	1.3 ± 1.4	0.61
Chronic smoking, no. (%)	5 (14)	2 (6)	7 (10)	0.43
Hypertension, no. (%)	14 (39)	10 (28)	24 (33)	0.45
Diabetes mellitus, no. (%)	2 (6)	0 (0)	2 (3)	0.47
Menopause, no./total (%)	19/34 (56)	21/36 (58)	40/70 (57)	> 0.99
Waist/hip ratio >0.85, no. (%)	19 (53)	17 (47)	36 (50)	0.81
aPL, no. (%)	14 (39)	11 (31)	25 (35)	0.46
LDL cholesterol, mmoles/liter	2.62 ± 1.04	2.42 ± 0.90	2.52 ± 0.97	0.39
HDL cholesterol, mmoles/liter	1.48 ± 0.35	1.63 ± 0.42	1.56 ± 0.39	0.11
Total cholesterol, mmoles/liter	4.80 ± 1.1	4.66 ± 0.97	4.73 ± 1.06	0.57
Triglycerides, mmoles/liter	1.55 ± 0.73	1.28 ± 0.68	1.41 ± 0.71	0.11
LDL cholesterol >2.6 mmoles/liter, no. (%)	15 (42)	17 (47)	32 (44)	0.90
Medications				
Low-dose aspirin, no. (%)	18 (50)	18 (50)	36 (50)	> 0.99
Prednisolone, no. (%)	25 (69)	23 (64)	48 (67)	0.62
Daily dose of prednisolone, mg	3.9 ± 3.3	3.4 ± 3.0	3.7 ± 3.1	0.50
Cumulative dose of prednisolone (first 12 months), gm	1.37 ± 1.1	1.27 ± 1.1	1.32 ± 1.1	0.72
Hydroxychloroquine, no. (%)	14 (39)	19 (53)	33 (46)	0.24
Azathioprine, no. (%)	17 (47)	16 (44)	33 (46)	0.81
Mycophenolate mofetil, no. (%)	4 (11)	2 (6)	6 (8)	0.67
Cyclosporin A, no. (%)	3 (8)	0 (0)	3 (4)	0.24

* Values are the mean ± SD unless otherwise indicated. SLE = systemic lupus erythematosus; IMT = intima-media thickness; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; AUC = area under the curve; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; aPL = antiphospholipid antibodies; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

were assessed at baseline and then at 2-month intervals. The cumulative SLEDAI scores over time (area under the curve [AUC]) were calculated. Adverse events during each visit were recorded.

Outcomes of interest and power calculation. The primary outcome of interest was the change in levels of homocysteine, hsCRP, and other endothelial markers from baseline to 12 months. Secondary outcomes included the change of carotid IMT from baseline to 24 months, new thrombotic events, and adverse effects. Assuming the difference in the levels of the biomarkers between the rosuvastatin and placebo groups of patients at 12 months was 20% (SD one-third of the mean), a sample size of 34 patients in each arm was required to detect this difference with an alpha error of 0.05 and a power of 0.80.

Assay of biomarkers. Biomarkers for cardiovascular risk prediction, homocysteine and hsCRP, were assayed by direct chemiluminescence (Siemens ADVIA Centaur CP System) and particle-enhanced immunonephelometry (Dade Behring BN ProsSpec System), respectively. Two biomarkers of vascular endothelial cell activation, specifically soluble VCAM-1 and P-selectin, were measured by enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems). Thrombomodulin, a marker for microvascular endothelial injury, was also measured using an ELISA kit from Diaclone Research. We assayed the levels of these endothelial biomarkers because we have previously shown that their levels were significantly elevated in SLE patients compared to controls (12). Moreover, levels of soluble VCAM-1, P-selectin, and thrombomodulin were shown to correlate significantly with SLE disease activity scores (12,13).

Measurement of the IMT of the carotid arteries. Atherosclerosis at 3 sites of the carotid arteries on both sides (common carotid, carotid bulb, internal carotid) was measured by B-mode ultrasound (Vivid 7 Dimension, GE Healthcare) using high-frequency 10-MHz linear array transducers. Carotid IMT was defined as the distance between the lumen–intima interface and the media–adventitia interface, which corresponded to the inner and outer echogenic lines seen on the B-mode ultrasound im-

age. The depth selection was maximized and the gain settings were optimized to visualize the posterior intima-media wall of the carotid artery. A single frame was identified during the end-diastolic phase. An approximately 2-cm segment was taken to measure the IMT. Two measurements in each sector were taken and the results were averaged. The investigator (CSL) who was responsible for carotid IMT measurement was blinded for the disease and treatment status of the participants.

Statistical analyses. Between-group (rosuvastatin and placebo) comparison of the baseline clinical characteristics and medications and the lipid levels was performed by the independent Student's *t*-test for continuous variable and chi-square test for categorical variables, respectively. Within-group (between baseline and 6 or 12 months) comparison of the levels of lipids and biomarkers and the change in carotid IMT (between baseline and 24 months) was made by the nonparametric Wilcoxon rank sum test. Levels of biomarkers between the rosuvastatin and placebo rosuvastatin arms at baseline were compared by the nonparametric Mann-Whitney U test. Levels of biomarkers at 6 and 12 months were compared with adjustment of their baseline values at 0 months, age, sex, SLEDAI score AUC (from baseline to 12 months), and medications (including use of low-dose aspirin, hydroxychloroquine, azathioprine, mycophenolate mofetil, and cyclosporin A, and the cumulative doses of prednisolone received in the first 12 months) by one-way analysis of covariance (ANCOVA). Bivariate correlation between the levels of biomarkers and SLEDAI scores was examined by Spearman's rank correlation test.

Statistical significance was defined as a 2-tailed *P* value less than 0.05. All statistical analyses were performed using the SPSS program, version 11.5, for Windows XP.

RESULTS

Patient enrollment and disposition. One hundred thirty-eight SLE patients with at least one vascular risk factor but no vascular ischemic symptoms were invited to a screening of subclinical atherosclerosis at the coronary or the carotid arteries by MDCT scan and B-mode Doppler ultrasound, respectively. Six patients declined screening, while 50 patients did not have atherosclerosis. Eight patients refused to join the study and 2 patients were excluded because they were having moderately active SLE. The disposition of patients is shown in Figure 1. Thirty-six patients were randomly assigned to receive rosuvastatin, while 36 other patients were assigned to receive placebo rosuvastatin tablets. Eighteen patients in each of the rosuvastatin and placebo rosuvastatin groups also received low-dose aspirin as part of randomization according to the original protocol. Three patients in the rosuvastatin arm and 2 patients in the placebo rosuvastatin arm did not complete the 12-month study. Three other patients died (1 of MI, 1 of lung cancer, and 1 of septicemia) during the open-label extension phase and could not have their carotid IMT repeated at 24 months.

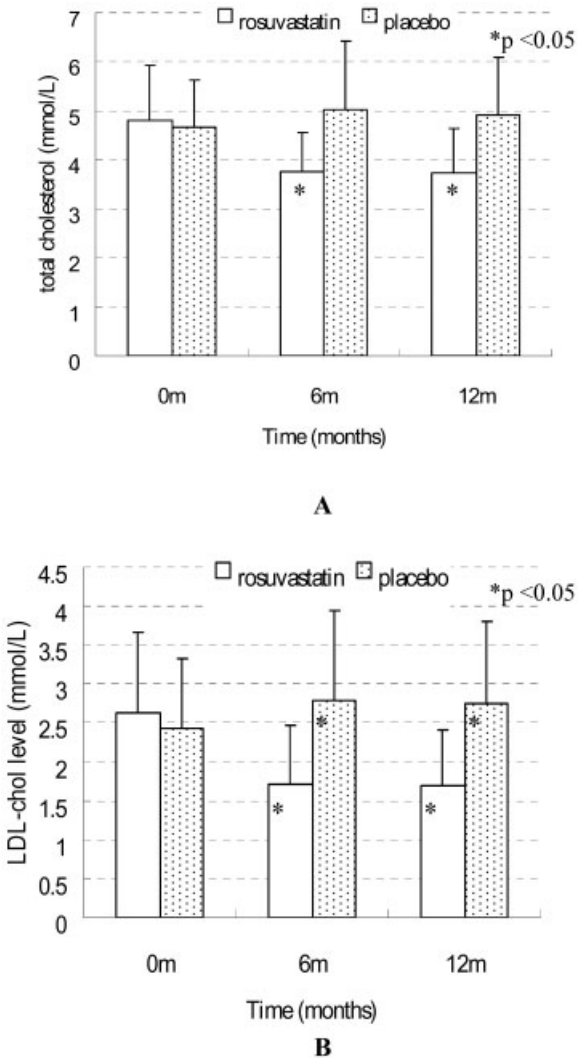

Figure 2. Change in total and low-density lipoprotein (LDL) cholesterol level over time. **A,** total cholesterol, **B,** LDL cholesterol. * = $P < 0.05$.

Baseline clinical characteristics, vascular risk factors, and medications. Seventy-two patients were studied (97% women). The mean ± SD age was 50.8 ± 9.7 years and the mean ± SD SLE duration was 11.8 ± 7.1 years. The mean ± SD carotid IMT was 0.67 ± 0.13 mm and the mean ± SD Agatston coronary calcium score was 30.9 ± 68. The prevalence of vascular risk factors was as follows: chronic smoking (10%), hypertension (33%), diabetes mellitus (3%), menopause (40 of 70; 57%), waist/hip ratio >0.85 (50%), LDL cholesterol >2.6 mmoles/liter (44%), and antiphospholipid antibodies (35%).

Table 1 shows the clinical characteristics, prevalence of vascular risk factors, mean ± SD carotid IMT values, disease activity scores, damage index, and medications of the recruited patients at study entry. No statistical differences in these parameters could be demonstrated between the rosuvastatin and placebo rosuvastatin groups of patients. The proportion of patients who were re-

Table 2. Change in levels of homocysteine, hsCRP, and endothelial markers over time*

Markers	Baseline, median (IQR)	Month 6, median (IQR)	Month 12, median (IQR)	P†
Homocysteine, μmoles/liter				
Rosuvastatin	13.6 (9.4)	12.6 (7.1)	13.4 (6.1)	0.48
Placebo	13.1 (4.6)	13.1 (4.8)	13.2 (3.9)	0.40
P‡	0.57	0.99	0.56	
hsCRP, mg/liter				
Rosuvastatin	1.26 (2.3)	0.94 (3.1)	0.88 (1.1)	0.02
Placebo	1.38 (3.0)	1.20 (4.0)	1.28 (4.3)	0.17
P‡	0.73	0.74	0.046	
Soluble VCAM-1, ng/ml				
Rosuvastatin	630 (590)	661 (650)	677 (510)	0.14
Placebo	724 (590)	694 (510)	701 (710)	0.19
P‡	0.26	0.89	0.56	
P-selectin, ng/ml				
Rosuvastatin	44.4 (23)	43.7 (28)	46.8 (23)	0.37
Placebo	44.8 (20)	47.7 (24)	48.7 (25)	0.07
P‡	0.89	0.76	0.66	
Thrombomodulin, ng/ml				
Rosuvastatin	0.91 (1.7)	0.76 (1.1)	0.84 (1.3)	0.04
Placebo	0.80 (0.6)	0.67 (0.6)	0.69 (0.7)	0.06
P‡	0.34	0.73	0.65	

* hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; VCAM-1 = vascular cell adhesion molecule 1.
† *P* values referred to comparison between baseline and 12 months in each group.
‡ *P* values referred to between-group comparison at different time points; values at 6 and 12 months were compared with adjustment for baseline values, age, sex, cumulative prednisolone dose, and systemic lupus erythematosus disease activity score in 12 months and medications (use of aspirin, hydroxychloroquine, and other immunosuppressive agents).

ceiving prednisolone, hydroxychloroquine, azathioprine, mycophenolate mofetil, and cyclosporin A at baseline was also similar. The cumulative prednisolone dose received and the SLEDAI score AUCs in the first 12 months were not statistically different between the two groups of patients.

Change in lipid levels. Figure 2 shows the change in mean lipid levels of patients who participated in the study. The total cholesterol level dropped significantly in rosuvastatin-treated patients at 12 months (mean ± SD 4.80 ± 1.14 mmoles/liter to 3.73 ± 0.91 mmoles/liter; $P < 0.001$), but not in the placebo rosuvastatin arm (mean ± SD 4.66 ± 0.97 mmoles/liter to 4.92 ± 1.18 mmoles/liter; $P = 0.07$). The LDL cholesterol level decreased significantly in the rosuvastatin group (mean ± SD 2.62 ± 1.04 mmoles/liter to 1.69 ± 0.72 mmoles/liter; $P < 0.001$), but increased significantly in the placebo group of patients (mean ± SD 2.42 ± 0.90 mmoles/liter to 2.75 ± 1.06 mmoles/liter; $P = 0.02$). There were no significant changes in the levels of high-density lipoprotein cholesterol and triglycerides in both arms. There was no effect of aspirin treatment on the lipid levels in both the rosuvastatin and placebo rosuvastatin groups of patients (data not shown).

Change in homocysteine and hsCRP levels. Table 2 shows the change in median hsCRP and homocysteine levels of our patients over time. At baseline, no significant differences in the levels of these two markers between the rosuvastatin and placebo rosuvastatin groups of patients were evident. The levels of homocysteine and hsCRP also did not differ significantly between users and nonusers of low-dose aspirin (data not shown). In the rosuvastatin group, the level of hsCRP decreased significantly at month 12 (1.26 mg/liter, interquartile range [IQR] 2.3 to 0.88 mg/liter, IQR 1.1 [30% decrease]; $P = 0.02$). No significant change in hsCRP level was observed in patients treated with placebo rosuvastatin ($P = 0.17$) (Figure 3A). The between-group difference in the hsCRP level was also significant at 12 months (by ANCOVA, $P = 0.046$) after adjustment for baseline values, cumulative prednisolone dose received, cumulative disease activity score, and use of aspirin, hydroxychloroquine, and other immunosuppressive medications.

The reduction in hsCRP level was more marked in patients with a baseline LDL cholesterol level of ≥2.6 mmoles/liter (1.93 mg/liter, IQR 5.7 to 1.04 mg/liter, IQR 1.2 [46% decrease]; $P = 0.04$) (Figure 3B). The levels of homocysteine did not change significantly in either group of patients.

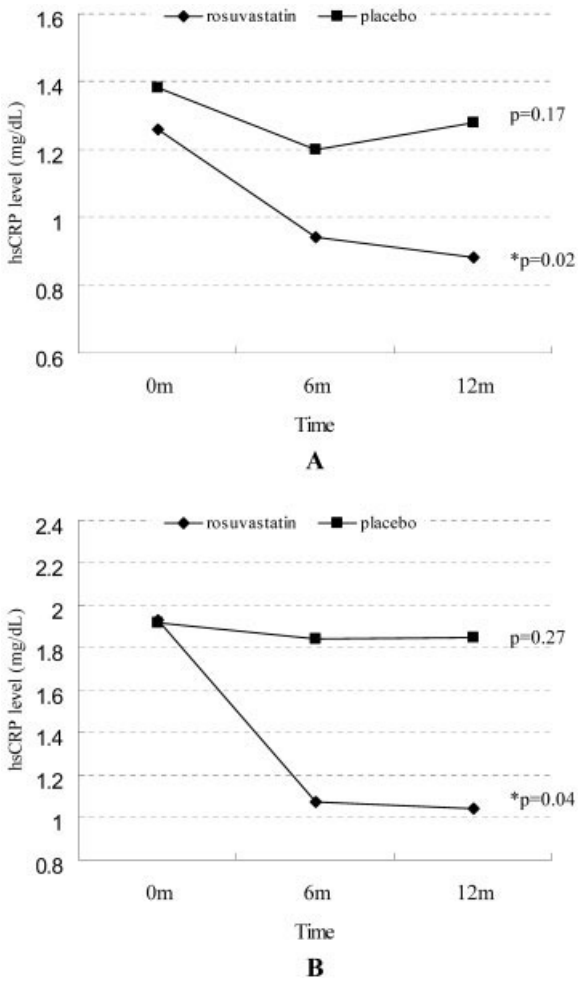

Figure 3. Change in high-sensitivity C-reactive protein (hsCRP) level over time in **A,** all patients, and **B,** those patients with a baseline low-density lipoprotein cholesterol level >2.6 mmoles/liter. * = $P < 0.05$.

Change in levels of the endothelial markers. Table 2 also shows the changes in median soluble VCAM-1, P-selectin, and thrombomodulin levels over time. In the rosuvastatin group of patients, a significant decrease in the level of thrombomodulin (0.91 ng/ml, IQR 1.7 to 0.84 ng/ml, IQR 1.3; $P = 0.04$) was observed. However, there were no statistically significant changes in the levels of other endothelial markers in patients treated with rosuvastatin or placebo rosuvastatin. The levels of these biomarkers at different time points were not significantly different between users and nonusers of low-dose aspirin (data not shown).

Correlation between disease activity and endothelial markers. The mean ± SD SLEDAI scores (AUC) over the first 12 months in the rosuvastatin and placebo rosuvastatin group of patients were 17.6 ± 20 and 22.7 ± 22 units, respectively, and the difference was not statistically significant ($P = 0.31$) (Table 1). A correlation study was performed between each of the endothelial markers assayed at 0, 6, and 12 months and the SLEDAI scores. A positive correlation was demonstrated between soluble VCAM-1 level and SLEDAI score ($\rho = 0.39$, $P < 0.01$), as well as between thrombomodulin level and SLEDAI score ($\rho = 0.21$, $P = 0.003$).

Subgroup analyses on patients with a SLEDAI score ≤2. As the levels of the endothelial markers correlated with disease activity of our patients, a subgroup analysis was performed for those with a SLEDAI score of ≤2 at 0, 6, and 12 months to reduce the possible influence of SLE activity on the levels of the biomarkers being studied (n = 25 for rosuvastatin, n = 24 for placebo). A significant decrease in the median levels of hsCRP ($P = 0.04$) and thrombomodulin ($P = 0.001$) was observed after rosuvastatin treatment in this subgroup (Table 3). On the other hand, the level of P-selectin increased significantly ($P = 0.04$) in the placebo rosuvastatin arm of patients.

Change in carotid IMT over 24 months. Table 4 shows the change in carotid IMT over 24 months in the participants. No statistically significant changes could be observed in either group of patients, but the IMT of the internal carotid arteries appeared to be decreased in rosuvastatin-treated patients (right side: mean ± SD 0.79 ± 0.32 to 0.72 ± 0.11 mm; $P = 0.12$, and left side: mean ± SD 0.80 ± 0.30 to 0.77 ± 0.12 mm; $P = 0.78$). In placebo-treated patients, there was a trend of progression of IMT values at all of the carotid artery sites studied.

Adverse events. Table 5 shows the adverse events experienced by our patients. Treatment was generally well tolerated. Numerically, more patients in the rosuvastatin arm reported gastrointestinal and neurologic symptoms, but the difference from the placebo arm was not statistically significant. There were no reports of hepatitis, skin rash, or rhabdomyolysis. One patient in the rosuvastatin group developed a transient ischemic attack, whereas 1 patient in the placebo group had a fatal MI during the open-label extension phase of the study.

DISCUSSION

This is a randomized, double-blind, placebo-controlled trial of the effect of rosuvastatin on hsCRP, homocysteine, several endothelial markers, and progression of carotid IMT in patients with stable SLE and subclinical atherosclerosis. We are able to demonstrate that low-dose rosuvastatin (10 mg/day) leads to a significant reduction in LDL cholesterol and hsCRP levels after 12 months of therapy. The reduction in hsCRP level is more marked in patients with a baseline LDL cholesterol of >2.6 mmoles/liter. In patients with very low disease activity (SLEDAI score ≤2), low-dose rosuvastatin also prevents the increase or leads to a decrease in endothelial markers P-selectin and thrombomodulin. After 24 months, the IMT

Table 3. Change in levels of homocysteine, hsCRP, and endothelial markers over time in those patients with a SLEDAI score ≤2 at 0, 6, and 12 months*

Markers	Baseline, median (IQR)	Month 6, median (IQR)	Month 12, median (IQR)	*P*†
Homocysteine, μmoles/liter				
Rosuvastatin	12.6 (3.8)	12.2 (4.0)	12.1 (3.3)	0.86
Placebo	13.3 (4.0)	13.1 (3.7)	13.3 (2.8)	0.78
P‡	0.29	0.98	0.54	
hsCRP, mg/liter				
Rosuvastatin	1.20 (2.3)	0.94 (2.7)	0.92 (1.1)	0.04
Placebo	1.14 (1.8)	0.99 (3.0)	1.21 (3.4)	0.23
P‡	0.65	0.09	0.20	
Soluble VCAM-1, ng/ml				
Rosuvastatin	520 (550)	583 (450)	610 (390)	0.43
Placebo	620 (480)	625 (460)	576 (800)	0.82
P‡	0.40	0.84	0.89	
P-selectin, ng/ml				
Rosuvastatin	44.4 (25)	43.6 (24)	45.6 (18)	0.38
Placebo	46.0 (20)	52.6 (23)	55.1 (26)	0.04
P‡	0.80	0.39	0.66	
Thrombomodulin, ng/ml				
Rosuvastatin	0.76 (1.2)	0.67 (0.8)	0.67 (1.0)	0.001
Placebo	0.79 (0.4)	0.62 (0.4)	0.64 (0.5)	0.27
P‡	0.50	0.81	0.63	

* hsCRP = high-sensitivity C-reactive protein; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; IQR = interquartile range; VCAM-1 = vascular cell adhesion molecule 1.
† *P* values referred to comparison between baseline and 12 months in each group.
‡ *P* values referred to between-group comparison at different time points; values at 6 and 12 months were compared with adjustment for baseline values, age, sex, cumulative prednisolone dose, and systemic lupus erythematosus disease activity score in 12 months and medications (use of aspirin, hydroxychloroquine, and other immunosuppressive agents).

Table 4. Change in carotid artery intima-media thickness over time

	Month 0, mean ± SD mm	Month 24, mean ± SD mm	Change, %
Right common carotid artery			
Rosuvastatin	0.54 ± 0.15	0.58 ± 0.11	+7.4
Placebo	0.54 ± 0.12	0.60 ± 0.11	+11
Right carotid bulb			
Rosuvastatin	0.65 ± 0.18	0.62 ± 0.14	−4.6
Placebo	0.63 ± 0.22	0.67 ± 0.13	+6.3
Right internal carotid artery			
Rosuvastatin	0.79 ± 0.32	0.72 ± 0.11	−8.9
Placebo	0.78 ± 0.20	0.79 ± 0.13	+1.3
Left common carotid artery			
Rosuvastatin	0.63 ± 0.14	0.66 ± 0.14	+4.5
Placebo	0.59 ± 0.13	0.65 ± 0.12	+10
Left carotid bulb			
Rosuvastatin	0.64 ± 0.13	0.67 ± 0.16	+4.7
Placebo	0.66 ± 0.18	0.71 ± 0.18	+7.6
Left internal carotid artery			
Rosuvastatin	0.80 ± 0.30	0.77 ± 0.12	−3.8
Placebo	0.78 ± 0.21	0.78 ± 0.16	0
Mean intima-media thickness (6 sites)			
Rosuvastatin	0.68 ± 0.20	0.67 ± 0.13	−1.5
Placebo	0.66 ± 0.18	0.70 ± 0.14	+6.1

Table 5. Adverse events*

	Rosuvastatin arm	Placebo arm
GI upset	5 (14)	3 (8)
GI bleeding	1 (3)	0 (0)
Postmenopausal bleeding	0 (0)	1 (3)
Minor infections	3 (8)	4 (11)
Myalgia/elevated CK level	0 (0)	0 (0)
Liver function abnormalities	0 (0)	0 (0)
Neurologic symptoms (e.g., dizziness, headache)	4 (11)	2 (6)
New vascular event	1 (3) (TIA)	1 (3) (MI)
Death	1 (3) (septicemia)	2 (6) (MI, cancer)

* Values are the number (percentage). GI = gastrointestinal; CK = creatinine kinase; TIA = transient ischemic attack; MI = myocardial infarction.

of the internal carotid arteries appeared to be decreased in rosuvastatin-treated patients.

On the other hand, our results also demonstrate that the levels of endothelial biomarkers such as soluble VCAM-1 and thrombomodulin correlate with SLE disease activity scores. Persistent disease activity in patients with SLE may contribute to progression of atherosclerosis because of the ongoing activation of the vascular endothelium. To eliminate the influence of disease activity on the levels of the endothelial markers, a subgroup analysis of those patients with very stable inactive disease revealed that rosuvastatin treatment significantly reduced the levels of hsCRP and thrombomodulin, indicating its potential efficacy in reducing cardiovascular risk.

In addition to their lipid-lowering effect, statins also possess a number of pleiotropic antiinflammatory and immunomodulatory actions that are potentially beneficial in slowing atherogenesis and reducing disease activity in autoimmune diseases such as SLE. Statins inhibit HMG-CoA reductase, an enzyme that converts HMG-CoA to mevalonate during cholesterol synthesis. The mevalonate pathway is involved in posttranslational modification of cell-signaling proteins during cell division and maturation (14). Statins prohibit proinflammatory effects and promote antiinflammatory activities through the direct inhibition/activation of chemokine-, cytokine-, and acute-phase reactant–driven intracellular signaling pathways (e.g., ERK-1/2, Rho, JAK/STAT-3, AMP-activated protein kinase, PI3K/Akt/NF-κB) in several cell types such as leukocytes, vascular endothelial cells, adipocytes, and hepatocytes (15). Therefore, by modulating the inflammatory intracellular pathways, statins are capable of slowing the process of atherosclerosis and reducing cardiovascular risk. Moreover, statins modulate the functions of cells that are involved in innate and adaptive responses and the production of cytokines and cellular adhesion molecules such as intercellular adhesion molecule 1, interleukin-6, tumor necrosis factor α, interleukin-1, and selectin levels (16). Finally, the statins also exhibit an antithrombotic effect by inhibiting platelet activation (17).

Statins have been studied in the murine lupus models. Atorvastatin has been shown to reduce autoreactive B cell activation, anti–double-stranded DNA production, proteinuria, and glomerular injury in (NZB $\times$ NZW)F_1 mice (18). In another murine model of SLE, simvastatin was shown to reduce lymphadenopathy, renal disease, and proinflammatory cytokine production (19). These effects were independent of the lipid-lowering action of simvastatin. In vitro experiments have also demonstrated that atorvastatin was able to restore some of the signaling defects in SLE T cells (20). However, a more recent study did not demonstrate efficacy of atorvastatin monotherapy in improving survival and reducing the severity of renal disease in the NZB $\times$ NZW mice (21).

Statins have also been attempted in human SLE. A case–control study has reported the efficacy of atorvastatin (20 mg/day) in improving endothelial function as measured by flow-mediated dilatation in 64 SLE patients (22). Another case–control study in 41 SLE patients showed the benefit of atorvastatin in lowering of the lipid levels after 2 months of treatment, but the CRP level did not change significantly (23). A recent randomized placebo-controlled trial showed that in 23 renal transplant recipients with SLE, administration of fluvastatin for a mean of 7.3 years reduced the risk of major cardiac events (24). Finally, a 2-year randomized, double-blinded, placebo-controlled trial of 200 SLE patients, presented in abstract form, indicated that atorvastatin (40 mg/day) may be superior to placebo in slowing the progression of carotid IMT, but there was no effect on progression of coronary calcium score or SLE disease activity (25).

There are several limitations of the current study. First, the sample size may not be large enough to show a significant difference in the levels of all of the endothelial biomarkers assayed. Second, a higher dosage of rosuvastatin (e.g., 20–40 mg/day) may be needed to suppress the endothelial markers better. Third, a higher dose of rosuvastatin and a longer period of observation are required to show a definite benefit of rosuvastatin treatment in reducing the progression of carotid atherosclerosis in patients with SLE. Nevertheless, our study provides evidence that treatment with potent statins is potentially beneficial in reducing cardiovascular risk in stable patients with SLE by decreasing the levels of hsCRP and thrombomodulin.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mok had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Mok, Wong, To, Lai, Lam.

Acquisition of data. Mok, Wong, To, Lai, Lam.

Analysis and interpretation of data. Mok, Wong, To, Lai.

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