Atorvastatin therapy improves endothelial-dependent vasodilation in patients with systemic lupus erythematosus: an 8 weeks controlled trial

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Introduction. Patients with systemic lupus erythematosus (SLE) have recognized reduction in endothelium-dependent vasodilation. Evidence demonstrates that statins are able to improve endothelial function independently on their hypolipemic action.

Objectives. To evaluate the efficacy of atorvastatin in improving vasodilation in SLE patients with and without conventional risk factors for coronary heart disease (CHD).

Patients and methods. Sixty-four SLE women, mean age 31 ± 8 yrs, received atorvastatin 20 mg/day during 8 weeks. Thirty-one patients in this intervention group did not have conventional risk factors for CHD, while 33 others had hypertension, dyslipidaemia and/or obesity. Twenty-four SLE control patients, mean age 34 ± 7.5 yrs, not receiving atorvastatin were followed during the same time period. High-resolution ultrasound was used to measure brachial artery diameter in resting conditions, during reactive hyperaemia and after sub-lingual glyceryl trinitrate (GTN). Measurements were performed at baseline and at the end of the study (8 weeks).

Results. Atorvastatin was associated with a significant increase in flow-mediated dilation (FMD) [3.8 (2.8–7.9%) vs 6.9 (4.2–10%), P < 0.001] while GTN-mediated dilation (GTND) was unaffected [20.9 (16.6–26.1%) vs 20.1 (16.6–25.4%), P = 0.514]. FMD increase was observed in patients with conventional risk factors [4.1 (3.1–8.7%) vs 6.5 (4–10%), P = 0.046] and also for those without conventional risk factors for CHD [3.6 (2.6–7.3%) vs 7.1 (4.5–10.9%), P = 0.001]. Resting brachial artery diameter also increased significantly in patients receiving atorvastatin (2.79 ± 0.30 mm vs 2.92 ± 0.40 mm, P < 0.001). No significant difference in artery diameter and FMD was seen in control patients at the end of the study. When compared to the control patients, atorvastatin treatment was associated with significant increase in resting diameter (+0.13 ± 0.1 mm vs −0.02 ± 0.07 mm, P < 0.001) and FMD (+1.9 ± 3.9% vs −0.3 ± 1.8%, P = 0.009).

Conclusion. Our results demonstrate that an 8-week 20 mg/day atorvastatin series improved endothelium-dependent vasodilation in SLE patients independently on the presence of conventional risk factors for atherosclerotic disease.

Key words: systemic lupus erythematosus, atorvastatin, endothelial function, vascular ultrasound, atherosclerosis.

Introduction

Classical study published by Urowitz et al. [1] in 1976 defined a bimodal mortality pattern in SLE patients. Death in the early stages of the disease is associated with disease activity and infection, while late mortality is usually the result of atherosclerotic disease. Atherosclerotic coronary heart disease (CHD) is now recognized as one of the main cause of morbidity and mortality in SLE patients in developed countries [2, 3]. In series of SLE patients, angina pectoris has been described in 4–12% of the patients, while myocardial infarction and sudden death have been reported in 5–16% and 1–8%, respectively [4–7]. Manzi et al. [5] demonstrated that the risk of coronary events among SLE patients aged 35–44 yrs old is 52 times higher when compared to sex and age-matched Framingham’s study controls. Other studies have estimated a 1.2–1.5% annual incidence rate for new coronary events in SLE patients [8, 9].

Conventional risk factors for CHD are highly prevalent among SLE patients. Despite their relevance for atherosclerosis pathogenesis, these factors alone seem not explain the high, intense and premature development of CHD in these patients [10, 11]. Other aspects related to the disease, namely chronic inflammation, antiphospholipid antibodies, chronic use of glucocorticosteroids, cytokines, homocysteine and anti-oxidized low density lipoprotein (LDL) antibodies, may all influence the prevalence of CHD among lupus patients [12, 13].

It is possible that the reported prevalence of coronary events underestimates the real frequency of CHD among lupus patients, since some patients may have asymptomatic disease. Different non-invasive techniques have been applied to detect subclinical CHD in these patients. Ultrasound studies in the brachial artery have demonstrated that flow-mediated vasodilation (FMD) is significantly reduced in SLE patients, independently on the presence of conventional risk factors for atherosclerotic disease [14].

In the last decades, statins have become one of the most effective strategies to reduce the risk of cardiovascular disease at both primary and secondary levels. Most of the evidence regarding this issue emphasizes the role of statins in reducing serum lipids. However, interesting new data have demonstrated clinical benefits of statins not directly associated with their hypolipemic action. Pleiotropic effects have been identified for these agents, including anti-inflammatory, immune modulator and anti-thrombogenic properties associated with improvement of endothelial function [15–17].

Statins inhibit 3-hydroxy-3-metil-glutaril-coenzime A (HMG-CoA) reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate during cholesterol synthesis. Mevalonate is also involved in post-translational modification (isoprenylation) of cell-signalling proteins (geranyl-geranyl pyrophosphate and Rho system proteins) involved in cell division and maturation. Inhibition of protein isoprenylation can act directly on endothelial function by increasing endothelial nitric oxide synthase expression [18, 19]. Statins also reduce angiotensin-II AT1 receptor expression contributing to a decrease in cellular proliferation, in the oxidative stress and in endothelin transcription, thereby improving vaso-reactivity [20]. Lipid-independent actions of statins also include increase in the number of endothelial cell precursors in the circulation [21].

Statins also have an important role in the modulation of cytokines and cell adhesion molecules reducing ICAM-1, IL-6, TNF-α, IL-1, E-selectin and P-selectin levels [22]. Triphosphate and diphosphate adenosine, which active platelets and leucocytes,
are hydrolyzed by endothelial CD39/ATPase. Statins are able to repair the metabolism of this enzymatic system and therefore reduce platelet activation [23]. Besides the anti-inflammatory and anti-thrombotic actions, statins have also been reported as immunomodulating agents by means of the inhibition of transcription of various genes induced by NF-κB and inhibition of interferon-β induced HLA class II expression on endothelial cells [16, 24]. Suppression of HLA class II expression contributes to prevent local T cell activation and this can minimize Th1-driven autoimmune [25].

Clinical data demonstration that SLE patients are at higher risk for precocious and more aggressive atherosclerotic disease and that endothelial dysfunction is remarkable at initial stages of the disease. Improvement of endothelial dysfunction could theoretically minimize atherosclerotic complications in this scenario. However, the effects of therapeutic interventions on the endothelial function in these patients have not been evaluated and no solid confirmation of this hypothesis is available in the literature.

In the present study we investigate the efficacy of atorvastatin in improving endothelium-dependent arterial dilation in SLE patients with and without conventional risk factors for atherosclerotic disease.

**Patients and methods**

**Patients and study design**

Patients with SLE were selected from the Rheumatology Outpatient Clinic at Minas Gerais Federal University Medical School Hospital. Sixteen healthy women with no conventional risk factor for CHD (mean age 29 ± 5 yrs) were included only for the evaluation of the ultrasound vascular measurement procedures. All individuals signed the informed consent approved by the institutional Ethics' Committee. Inclusion criteria were: female sex, SLE according to the American College of Rheumatology revised classification criteria [26], disease diagnosis equal or greater than 1 yr, age >18 yrs and regular menstruation. Exclusion criteria included: current or past use of hypolipemic drugs in the last six months, menopausal status, diabetes mellitus, serum creatinine above 1.2 mg/dl, pregnancy, smoking status (last 12 months), family history of CHD, skeletal myopathic disease and/or elevated creatinine phosphokinase (CK), hepatic disease and cyclosporine use. Family history of CHD was defined as the presence of clinical CHD or sudden death in first-degree relatives at ages less than 55 yrs and 65 yrs for men and women, respectively. Hypertension was defined as blood pressure higher than 140 × 90 mmHg or current use of antihypertensive medications.

Other conventional risk factors for CHD were defined as follows. Obesity: body mass index (BMI) over 30 kg/m² and/or presence of abdominal obesity, considered as abdominal circumference above 88 cm. Diabetes mellitus: fasting plasma glucose higher than 126 mg/dl or use of oral hypoglycemic agents or insulin. Dyslipidaemia: high density lipoprotein (HDL) cholesterol serum levels <40 mg/dl or low density lipoproteins (LDL) cholesterol serum levels >130 mg/dl or total cholesterol serum levels >200 mg/dl or triglyceride serum levels >200 mg/dl. Menopause: amenorrhea for more than 1 yr or use of hormonal replacement therapy.

SLE disease activity and damage were measured using SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) [27] and SLICC (The Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index for Systemic Lupus Erythematosus) [28], respectively.

A total of 91 patients with SLE were included in the study. Three patients were excluded for reasons not related to the therapeutic protocol and 88 completed the study follow-up of 8 weeks. Patients were divided in two groups. Intervention group consisted of 64 patients who received atorvastatin 20 mg/day during 8 weeks. Thirty-three patients in the intervention group had hypertension, dyslipidaemia and/or obesity, while the remaining 31 did not have any conventional risk factor for CHD. The control group comprised of 24 SLE patients followed in the same period without atorvastatin. To reinforce and to check adherence to the protocol, phone calls or personal contacts were performed 30 days after the beginning the study and atorvastatin tablets were counted at the end of the study. At baseline and at the end of the 8-week period, all 88 participants underwent complete clinical examination, brachial artery ultrasound and blood sampling for laboratory analysis.

**Methods**

**Vascular measurements**

Vascular studies were performed at room temperature (25–28°C) using high-resolution ultrasound equipment, vascular color echoDoppler with flow mapping (ACUSON, Mountain View – California, USA) and multiple-frequency linear 7 MHz transducer. All patients were evaluated between 8:00 and 10:00 am, after 12 h overnight fast. Antihypertensive medication was stopped 24 h before the study. All exams were performed by the same examiner (TPN) following previously described technique [29] and the guidelines for ultrasound assessment of endothelial-dependent flow-mediated dilation (FMD) of the brachial artery [30]. Briefly, patients were positioned supine with the arm in a comfortable position for scanning the brachial artery 7 cm above the antecubital fossa in the longitudinal plane. Speed flow and diameters were scanned and recorded on a super VHS videotape for measurement at baseline and after a flow stimulus. To create a flow stimulus in the brachial artery, a sphygmomanometer cuff placed on the forearm was inflated to 230–250 mmHg during 5 min and then released, thereby inducing reactive hyperaemia and increased flow. At about 50–60 s after cuff release, longitudinal scan of the artery was recorded to measure flow and artery diameter. After 1.5 min, further measurement was taken at rest and 3 min after sublingual spray of 400 μg GTN. Recorded images were later analysed by the examiner without any information on the patient’s identification.

The median values for resting diameter and FMD in 16 healthy women were 2.76 mm (range 2.4–3.0) and 10.52% (range 6.89–12.64), respectively. Brachial artery ultrasound was performed as described and then repeated 7 days later in eight of them in order to evaluate reproducibility of the procedure. We observed very good correlation between the two measurements for both resting artery diameter and FMD. The intra-class correlation coefficient for resting diameter and FMD were 0.98 (95% CI, 0.92–0.99) and 0.80 (95% CI, 0.39–0.95), respectively.

**Laboratory tests**

The following laboratory exams were performed according to standard routine techniques: complete blood count, creatinine, fasting glucose, total cholesterol, HDL, LDL and VLDL cholesterol, triglycerides, creatine phosphokinase (CPK) and serum complement (C3, C4 and CH50) levels, as well as liver function tests and urinalysis. Anti-dsDNA antibodies were detected by indirect immunofluorescence using Crithidia luciliae as substracte, and anticardiolipin antibodies were determined by enzyme immunoassay. Anticardiolipin antibodies were considered positive when higher than 20 GPL or 11 MPL. Homocysteine and lipoprotein-a serum levels were measured by liquid chromatography (reference range <15 μmol/l) and immunonephelometry (Dade Behring, reference range <30 mg/dl), respectively.

**Statistical analysis**

Statistical packages Minitab 13.2 and SPSS for Windows 12.0 were used. Descriptive analyses were performed and data were presented as mean, median, s.d. and percentile. Normal
distribution of the study variables was tested using Kolmogorov–Smirnov test. Paired and independent Student’s t-test, or Wilcoxon and Mann–Whitney’s tests were applied according to the normal or non-normal distribution. Spearman and Pearson’s correlation analyses were used to investigate potential association between variables. Multiple linear regression models were then designed to determine the most significant associations. Significance level was set as \( P < 0.05 \).

**Results**

Patients were classified as white (64.8%) and non-white (35.2%), with mean age of 32 ± 8 yrs and mean disease duration of 8.9 ± 4.8 yrs. SLEDAI and SLICC scores ranged from 0 to 18 (mean 14.6) and from 0 to 4 (mean 1.06), respectively. Along with the disease, neurological manifestations were registered in 11 patients (12%), vasculitis in 36 (40%), nephritis in 49 (55%), Raynaud’s phenomenon in 25 (28%), and antiphospholipid antibody syndrome in five patients (5%). At the moment of the study, eight patients (9%) had anti-dsDNA antibodies and 11 (11%) had anticardiolipin antibodies (seven IgG and three IgM class). None of the patients had conferred coronary or cerebrovascular event. Most of the patients (72 individuals, 81.8%) were on regular use of prednisone. Fifty-four patients (61%) were on regular use of atorvastatin. Revised Framingham Risk Scores for CHD in seven patients (7.9%). Eight patients were also on regular use of immunosuppressive agents [azathioprine in 20 patients (22.7%); chloroquine diphosphate and 46 (52%) were receiving additional prednisone. Fifty-four patients (61%) were on regular use of prednisone.

Within the 8-week treatment interval patients receiving atorvastatin had a significant increase in brachial artery resting diameter and FMD as compared to the control group (+0.15 ± 0.10 mm \( \text{vs} \) −0.02 ± 0.07 mm, \( P < 0.001 \); +1.9 ± 3.9% \( \text{vs} \) −0.3 ± 1.8%, \( P = 0.009 \), respectively) (Table 2). Atorvastatin did not significantly affect GTN-mediated dilation in the 64 SLE patients [baseline 20.9 (16.6–26.1%) \( \text{vs} \) 8th week 20.1 (16.6–25.4%), \( P = 0.514 \)].

Table 3 shows haemodynamic parameters of the 64 patients at baseline and after 8 weeks of atorvastatin. There were no significant changes in mean systolic BP (119.39 ± 118.21 mmHg; \( P = 0.81 \)) or diastolic BP (74.44 ± 72.82 mmHg; \( P = 0.68 \)) following atorvastatin therapy.

Within the 8-week treatment interval patients receiving atorvastatin had a significant decrease of total cholesterol (162 ± 36 mg/dl \( \text{vs} \) 128 ± 34 mg/dl, \( P < 0.001 \)), LDL-cholesterol (92 ± 30 mg/dl \( \text{vs} \) 61 ± 29 mg/dl, \( P < 0.001 \)), triglycerides (115 ± 55 mg/dl \( \text{vs} \) 97 ± 45 mg/dl, \( P < 0.001 \)) and homocysteine level [8.9 (6.8–10.74 µmol/l) \( \text{vs} \) 7.4 (6.6–9.17 µmol/l), \( P = 0.011 \)]. In contrast, atorvastatin did not significantly affect serum levels lower and mean diastolic blood pressure was significantly higher in the control group as compared to the intervention group.

At the end of 8 weeks, there was a significant increase in FMD in the 64 patients receiving atorvastatin [3.8 (2.7%–7.9%) \( \text{vs} \) 6.9 (4.2%–10.7%), \( P = 0.001 \)] (Fig. 1). The analysis of subgroups of 26 patients with and 38 patients without dyslipidaemia showed both groups achieved a significant increase in the FMD after atorvastatin [3.84 (2.62–7.7%) \( \text{vs} \) 7.14 (4.52–10.52%), \( P = 0.015 \) and 3.84 (3.12–9.09%) \( \text{vs} \) 6.45 (4.16–10.71%), \( P = 0.006 \), respectively]. Statistical analysis showed the increase in FMD after atorvastatin in both subgroups were not significantly different (2.41 ± 4.30% \( \text{vs} \) 1.84 ± 3.62%, \( P = 0.551 \)). In contrast, no significant difference in FMD was seen between baseline and at the end of the study for control group [4.7 (3.2%–7.9%) \( \text{vs} \) 4.1 (3.5%–7.0%), \( P = 0.426 \)] (Fig. 2).

Atorvastatin treatment was associated with a significant increase in brachial artery baseline diameter (baseline 2.79 ± 0.30 mm \( \text{vs} \) 8th week 2.92 ± 0.40 mm, \( P = 0.001 \)). No significant difference in brachial artery baseline diameters was seen for patients in the control group (2.92 ± 0.35 mm \( \text{vs} \) 2.90 ± 0.36 mm, \( P = 0.164 \)). Accordingly, within the 8-week study interval patients receiving atorvastatin had a significant increase in brachial artery resting diameter and FMD as compared to the control group (+0.15 ± 0.10 mm \( \text{vs} \) −0.02 ± 0.07 mm, \( P < 0.001 \); +1.9 ± 3.9% \( \text{vs} \) −0.3 ± 1.8%, \( P = 0.009 \), respectively) (Table 2). Atorvastatin did not significantly affect GTN-mediated dilation in the 64 SLE patients [baseline 20.9 (16.6–26.1%) \( \text{vs} \) 8th week 20.1 (16.6–25.4%), \( P = 0.514 \)].

![Figure 1](http://rheumatology.oxfordjournals.org/)

**Table 1.** Demographic characteristics and baseline risk factors for CHD in 64 SLE patients treated with atorvastatin (intervention group) and in 24 SLE patients not receiving atorvastatin (control group)

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin Group (N = 64)</th>
<th>Control SLE patients (N = 24)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>32 ± 8</td>
<td>34 ± 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>8.5 ± 4.9</td>
<td>8.5 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158 ± 5.8</td>
<td>159 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 ± 4.2</td>
<td>26.9 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117 (110–127)</td>
<td>120 (110–130)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74 (70–80)</td>
<td>80 (78–83)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>162.5 ± 36</td>
<td>162 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>92 ± 30</td>
<td>95 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>47 ± 12</td>
<td>41 ± 8</td>
<td>0.049</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>115 ± 55</td>
<td>196 ± 119</td>
<td>NS</td>
</tr>
<tr>
<td>SLEDAI score</td>
<td>4.4 ± 5</td>
<td>3.3 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>SLICC score</td>
<td>1.1 ± 1.2</td>
<td>0.79 ± 0.77</td>
<td>NS</td>
</tr>
</tbody>
</table>
for HDL-cholesterol (47.28 ± 12 mg/dl vs 47.39 ± 12 mg/dl, P = 0.93) and lipoprotein-a [18.50 (9.0–34.20 mg/dl) vs 16.95 (9.0–37.65 mg/dl), P = 0.83]. No significant difference was observed in the biochemical parameters in the control group during the study time course (data not shown).

Surprisingly, a significant decrease in SLEDAI mean scores was observed for patients in the intervention group at the end of the study (4.47 ± 5.0 vs 3.08 ± 3.6, P < 0.001) while patients in the control group experienced significant increase in their mean disease activity scores (3.33 ± 3.95 vs 4.33 ± 4.17, P = 0.02).

Twenty-eight patients (43.7%) receiving atorvastatin presented decrease in the SLEDAI score. Vasculitis improved in three cases, arthritis in six, rash in five, alopecia in eight, mucosal ulcers in two and pleurisy in one patient. The changes in laboratory tests after atorvastatin included: decrease in proteinuria (three cases), in haematuria (one case) and in pyuria (two cases). Increase in the serum complement level was observed in eight patients, increase in platelets count in one, increase in leucocyte count in one and in another one the anti-ds DNA became negative.

It is important to point out that no significant difference in the dose of oral prednisone was observed between baseline and the end of the study for both, intervention [7.5 mg (2.5–20 mg) vs 7.2 (2.4–19.2 mg); P = 0.52] and control groups [5 mg (2.5–20 mg) vs 4.6 mg (2.3–18.4 mg); P = 0.21].

No significant difference was observed in the increase in FMD after 8-week atorvastatin therapy in patients with and those without chloroquine (2.2 ± 3.06% vs 1.4 ± 4.99%, P = 0.47).

None of the patients in the atorvastatin group needed to be withdrawn due to adverse effects of the study drug. Three patients presented mild headache and two others reported mild myalgia that disappeared despite continued use of the medication. None of latter patients had abnormal creatine phosphokinase serum levels. One patient complained of mild arthralgia for one week at the beginning of the treatment and this symptom also spontaneously disappeared.

**Discussion**

To our knowledge, this is the first study to evaluate the effect of atorvastatin on endothelial dysfunction in SLE patients. Our data demonstrated that an 8-week period atorvastatin treatment was associated with a significant increase in FMD in SLE patients. The observed effect of atorvastatin on FMD was independent on the presence of conventional risk factors for CHD and suggests that atorvastatin improves endothelial function in SLE patients.

The effect of atorvastatin on FMD in our study was independent on baseline serum lipids levels, corroborating previous studies in patients with hypertension [31], diabetes mellitus [32] and dyslipidaemia [33], and supporting the notion that the endothelial benefits of atorvastatin are independent of the reduction in serum lipids levels. In the present study we also confirmed previous findings of reduced FMD in SLE patients as compared to healthy controls, suggesting significant endothelial dysfunction in SLE patients [14, 34, 35].

Literature evidence supports the notion that statins significantly reduce the risk of future cardiovascular events independently on the LDL-cholesterol levels in clinical scenarios with increased risk for CHD as in patients with myocardial infarction and diabetes mellitus [36]. Bruce has suggested that about 25–35% of the SLE patients should be on statins aiming to maintain LDL-cholesterol levels below 100 mg/dl [2]. Taking into consideration the pleiotropic effects of statins on endothelial function, supported by the present findings, and also the high risk for CHD seen in patients with SLE, one could speculate that a higher percentage of patients with SLE could benefit from such intervention.

The use of atorvastatin in our study was associated with significant improvement in flow mediated arterial dilation, homocysteine serum levels reduction and decrease in SLEDAI. The effect of atorvastatin on FMD in our study was independent on the LDL-cholesterol levels in clinical scenarios with increased risk for CHD as in patients with myocardial infarction and diabetes mellitus [36]. Bruce has suggested that about 25–35% of the SLE patients should be on statins aiming to maintain LDL-cholesterol levels below 100 mg/dl [2]. Taking into consideration the pleiotropic effects of statins on endothelial function, supported by the present findings, and also the high risk for CHD seen in patients with SLE, one could speculate that a higher percentage of patients with SLE could benefit from such intervention.

The use of atorvastatin in our study was associated with significant improvement in flow mediated arterial dilation, homocysteine serum levels reduction and decrease in SLEDAI.
scores, demonstrating that statins in SLE patients can bring benefits beyond their hypolipemic action. However, long-term multicentric placebo-controlled double-blinded studies including higher number of patients are required in order to reach solid evidence and to precisely define the recommendation for statins use in SLE patients, as those published on diabetes mellitus.

Statins are among the most prescribed medications and have been considered very safe with a favorable risk-benefit relationship. In the literature there are a few isolated case reports of lupus-like syndrome induced by statins. One case was associated with autoimmune hepatitis [37], two other cases had pulmonary involvement [38, 39] and the others were associated with skin lesions similar to sub-acute lupus [40] and dermatomyositis [41]. In contrast with common autoimmune reactions associated with other drugs, cutaneous manifestations associated with statin usually occurred many months after the beginning of the treatment and the autoantibodies, when present, remained positive months after discontinuation of the treatment. This emphasizes that the causal relation between statins and autoimmune disease is still controversial and hard to prove. The duration of our study was not suitable to evaluate long-term adverse effects associated with atorvastatin use and this limitation needs to be pointed out.

In the present study, only six patients had mild and transitory adverse effects related to atorvastatin use and none of them justified discontinuation of the therapy. None of the patients had significant increase in serum levels of creatine phosphokinase, glutamic-oxaloacetic transaminase and glutamate pyruvate transaminase. Abud-Mendoza et al. [42] have also not observed significant adverse effects after use of statins (simvastatin or atorvastatin) in patients with diverse rheumatic inflammatory diseases refractory to conventional treatment. The authors concluded that statins are safe to be used in patients with SLE and their benefits surplus their risks.

Unexpectedly, we observed significant reduction in SLEDAI scores in patients receiving atorvastatin, while significant increase was found in the control group. It is important to mention that we did not control prednisone doses or the use of immunosuppressive drugs during the study and the medications were prescribed according the necessity. However, we did not find significant difference in the prednisone mean dose between the baseline and after 8 weeks in both the atorvastatin and control groups. Therefore, this interesting finding must be explored in further studies specially designed for that purpose.

Our finding of increased brachial artery resting diameters after atorvastatin use was somewhat unexpected. The fact that patients in the control group did not present any significant difference in their artery resting diameters supports the interpretation that this change was not due to plain temporal variation. Potential effect of a hyperdynamic state was also ruled out since heart frequency and flow speed did not change significantly between the two measurements. One possible explanation for the increase in arterial resting diameter could be higher production of vasodilator products, such as nitric oxide, lower expression of vasoconstrictor substances, such as endothelin, and down-regulation of inflammatory gene transcription factors in vascular smooth muscle cells, all of these known to be induced by atorvastatin [18, 20, 43].

Conventional risk factors classically associated with atherosclerosis in the general population may not be sufficient to discriminate the risk of atherosclerosis in lupus patients. In the present study we observed reduced FMD in SLE patients independently on the presence of conventional risk factors for CHD, confirming our previous findings [14].

Homocysteine causes oxidative stress, endothelial lesion and increases thrombogenesis. One observational study suggested that even mild or moderate elevations in homocysteine serum levels are associated with increased risk for CHD [44]. However, a recent prospective randomized study concluded that the reduction in homocysteine serum levels induced by combined supplementation of vitamin B12 and folic acid did not reduce the risk of cardiovascular events in patients with previous CHD [45].

Schroecksnadel et al. [46] have demonstrated that atorvastatin inhibits homocysteine production by human mononuclear cells in vitro by inhibition of cellular proliferation. Dobraniu et al. [47] observed that atorvastatin reduced homocysteine levels in about 19% in patients with coronary disease.

In the present study, atorvastatin use was also associated with significant reduction in homocysteine serum levels. Further multicentric studies will be needed to confirm these findings and also to investigate whether atorvastatin-induced homocysteine level reduction may translate into lower risk for major cardiovascular events.

In conclusion, the present study showed that an 8-week period atorvastatin treatment improved endothelial function measured by brachial artery ultrasound in SLE patients, independently on the presence of risk factors for CHD. These findings suggest that atorvastatin may be useful to prevent atherosclerotic cardiovascular complications in this clinical scenario. These preliminary findings must be confirmed by long-term multicentric studies designed to precisely define the recommendation for statins in SLE patients.

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References

Atorvastatin and endothelial function in SLE patients

1565


