Low dose of simvastatin reduces disease activity and improves endothelial function in patients with SLE

Sirs,

I read with the interest paper by Castejon *et al*. on the improvement of arterial stiffness and reduction of endothelial progenitor cells after short term treatment with low dose of atorvastatin in patients with systemic lupus erythematosus (1). The paper addresses the very important question on utility of atorvastatin and more general statins in patients with SLE. The authors observed reduction of arterial stiffness after 8 weeks of treatment together with reduction of cellular adhesion molecules (VHGF and sVCAM) and reduction of circulating endothelial progenitor cells. To support this interesting observation, I would like to present the results with simvastatin that was given to similar SLE patients with low dose (20 mg nocte) for only 28 days. I excluded from the study patients with atherosclerosis on the basis of IMC measurement, where values more than 0.9 mm were recognised as abnormal suggesting subclinical atherosclerosis. The other main exclusion criterion was hypercholesterolemia defined as total cholesterol >200 mg/dl or LDL cholesterol >130 mg/dl. After selection, 15 female SLE patients with moderate disease activity were included to the study (Table I).

Measurement of flow mediated dilation (FMD), laboratory tests and cellular adhesion molecules (ICAM, VCAM, sP, sE and sL-selectins) levels were assessed twice - before the study and after 4 weeks of treatment with simvastatin.

Analyses were performed using the STATISTICA 10.0 PL (StatSoft). All data are expressed as means with standard deviations. Distribution of variables was evaluated by the Shapiro-Wilk test. Homogeneity of variances was assessed by the Levene test. To compare two dependent groups (before and after treatment) the non-parametric U Mann-Whitney test was used. A p value of less than 0.05 was considered statistically significant.

Short treatment with simvastatin resulted in significant improvement in FMD and small but significant reduction of disease activity. Improvement in endothelial function goes together with reduction of ICAM and sP-selectin. I failed to observe the reduction of lipids parameters, as none of the parameters studied (total cholesterol LDL, HDL and LDL/HDL ratio) did change significantly (Table II).

Table I. Characteristics of patients and results of the simvastatin treatment.

Patients' characteristics (n=15)

Parameter	mean	SD	median	min.	max.
age (years)	36	10	35.5	20	62
gender	100% female				
race	100% Caucasian				
Disease duration (months)	47	45	24	3	144
BMI (kg/m^2)	23.5	3.1	22.5	18.8	29.3
Hemoglobin (g/dL)	12.2	1.8	12.5	8.3	14.4
Erytrocyte (x10^{12}/L)	4.17	0.53	4.18	2.86	4.91
Leukocyte (x 10^9/L)	6.72	2.36	6.24	3.30	11.66
Platelets (x 10^9/L)	210.6	66.2	194.5	145.0	393.0
CPK (U/L)	31.2	12.1	32.0	12.0	56.0
eGRF (ml/min/1.73m^2)	100.0	24.5	108.1	46.6	132.1

Concomitant treatment

		mean	SD	median	min.	max.
Steroids	(n= 14; 94%)	19.7	10.4	20.0	15	20
Chloroquine	(n=4; 27%)					
Mycophenolate mofetil	(n=5; 33%)					
Azathioprine	(n=3; 20%)					

Effects of simvastatin on lipid parameters, disease activity and adhesion molecules in patients with SLE

parameter	before statins	after statins	significance
Disease activity (SLEDAI)	6.31 ± 2.91	4.81 ± 2.45*	p<0.05
Total cholesterol	157.49 ± 35.41	167.89 ± 50.1	ns
LDL cholesterol	126.74 ± 35.91	130.51 ± 62.25	ns
HDL cholesterol	50.31 ± 9.7	53.25 ± 10.14	ns
FMD (%)	9.8 ± 0.8	13.0 ± 0.6*	p<0.05
GMD (%)	20.4 ± 0.082	21.6 ± 7.0	p<0.05
ICAM (ng/mL)	1072 ± 364	869 ± 311	p<0.05
VCAM (ng/mL)	2025 ± 144.67	1559 ± 990	ns
sE-selectins (ng/mL)	316 ± 92	319 ± 167	ns
sP-selectins (ng/mL)	68.5 ± 26.5	54.4 ± 16.3	p<0.05
sL-selectins (ng/mL)	1030 ± 301	911 ± 205	ns

BMI: body mass index; CPK: kinase phosphocreatine; eGFR: glomerular filtration rate; FMD: flow mediated dilation; GMD: nitroglycerin mediated dilation; ICAM: intracellular adhesion molecule; VCAM: vascular cell adhesion molecule; ns: non-significant.

The results of the study largely confirmed the observation by Castejon *et al*. What is of special interest is that the observed improvement in adhesion molecules and endothelial function (improvement in FMD) occurred in normocholesterolemic, atherosclerosis-free, relatively young population. The immunomodulatory activity of simvastatin that appeared before changes in cholesterol might be apparent, and supports the thesis on pleiotropic activity of statins in lupus patients (2). This is in line with the results observed in our previous study, where improvement of FMD and reduction of disease activity were also observed in non-selected population (normocholesterolemic and hypercholesterolemic together) (3, 4). It may be speculated that reduction of ICAM (endothelial intracellular adhesion molecule B; CD 54) observed in our study is responsible not only for the improvement of endothelial function, but also (at least partially) for reduction of disease activity. Interaction between ICAM and its ligand lymphocyte function associated antigen (LFA-1) is a key phenomenon in lymphocyte homing and leukocyte trafficking to the inflammation site (5). Interaction between LFA-1 and ICAM-1 is a part of normal immune response providing strong costimulatory effect to T cells, independently from CD28 activation (6). Reduction of this arm of immune response might be responsible for reduction of disease activity observed in the study.

The study has however some major limitations. The relatively small group of subjects studied may have a strong impact on statistical analyses; final calculations may therefore not be free of bias. The results should be confirmed in larger group of patients before final conclusions can be drawn.

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