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Statin therapy in lupus-mediated atherogenesis: two birds with one stone?

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Abstract

The atherosclerotic process is accelerated in patients with systemic lupus erythematosus (SLE). In addition to a robust lipid-lowering effect, various immunomodulatory functions have been ascribed to statins. By virtue of the latter they may be able to reduce atherosclerotic vascular disease in SLE by inhibiting immune activation within the arterial wall and by attenuating lupus activity. The effects of statins on SLE as well as on lupus-mediated atherogenesis in vivo are discussed in this viewpoint.

ATHEROGENESIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Now that it has been firmly established that systemic lupus erythematosus (SLE) is associated with cardiovascular disease (CVD), ^{1–3} focus is shifting towards composing and implementing atheroprotective strategies as well as elucidating underlying mechanisms of lupus-mediated atherogenesis. With regard to the latter, clinical cohort studies have revealed that traditional atherosclerotic risk factors (eg, dyslipidaemia, hypertension, diabetes) do not fully account for the CVD susceptibility in patients with SLE. ⁴ Additional risk factors have been suggested to play a part, such as impaired renal function, an imbalance between atherogenic injury to the endothelium and its subsequent repair and effects of immune cell activation and inflammation. ⁵ Nevertheless, traditional risk factors are more prevalent in patients with SLE and appear to still have a major role in lupus-enhanced atherogenesis. For instance, both hypercholesterolaemia and hypertension were independently associated with accelerated atherosclerosis in several SLE cohorts. ^{6–8}

The excessive CVD risk in SLE justifies increased vigilance and lowers the threshold for initiating therapeutic interventions aimed at improving those risk factors that can be modified. However, Urowitz *et al*⁹ prospectively followed up 576 patients with SLE and while 261 patients (45%) had hypercholesterolaemia, only 74 of these 261 patients (28%) were prescribed a lipid-lowering agent. In contrast, 241/576 (42%) patients were hypertensive, of whom 232 (96%) were receiving antihypertensive treatment. CVD is a major source of morbidity and mortality in SLE and while dyslipidaemia contributes to

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lupus-enhanced atherogenesis, the limited data available on lipid-lowering treatment in patients with SLE are indicative of undertreatment.

STATIN THERAPY IN SLE

A reduction in levels of low-density lipoprotein cholesterol by treatment with statins constitutes one of the cornerstones in the prevention of CVD. Unfortunately, statins have not yet been evaluated in SLE in a placebo-controlled trial with solid end points. In addition to its effects on lipid metabolism, several anti-inflammatory effects have been ascribed to statins.¹⁰ For instance, statins reduce expression of adhesion molecules and thereby attenuate adhesion and extravasation. Furthermore, they inhibit expression of major histocompatibility complex class II and costimulatory molecules by antigen-presenting cells and prevent antigen presentation to CD4 T cells.¹¹ By virtue of the various immunomodulatory functions exerted by statins, they may be able to reduce atherosclerotic vascular disease in SLE by reducing immune activation within the arterial wall and also by attenuating lupus activity.

Effect of statin therapy in animal models of SLE

The first preclinical study investigating the role of statin therapy in an animal model of lupus was performed by Lawman *et al*¹² (see table 1). Treatment of New Zealand Black/New Zealand White (NZB/NZW) mice with atorvastatin (30 mg/kg/day) resulted in a reduction in serum IgG anti-dsDNA antibodies and diminished the progression of lupus nephritis. Thus, atorvastatin reduced glomerular hypercellularity, interstitial infiltrates and was associated with a smaller increase in glomerular matrix. These beneficial effects could not be reproduced, however, by Graham *et al*¹³ in a study where NZB/NZW mice were treated with atorvastatin at a lower dose (10 mg/kg/day) for a longer period of time. Atorvastatin neither had significant impact on the production of anti-dsDNA antibodies nor on the age of onset or the severity of proteinuria. One explanation for this apparent discrepancy relates to the atorvastatin dose. It should be noted that a dose of 30 mg/kg/day exceeds the clinical dose. Statins typically do not affect serum lipid levels in mice and although Graham *et al* did not observe any differences in serum cholesterol levels, Lawman *et al* reported a significant 34% decrease in atorvastatin-treated NZB/NZW mice, indicative of high dosing in the latter study. Consistent with the findings of Graham *et al*, the effects of pravastatin on lupus activity were limited in a recent study in MRL-Fas^{lpr} mice.¹⁴ Although pravastatin lowered serum titres of IgG anti-DNA antibodies, it had no effect on glomerular and tubular damage, leucocyte infiltration in the kidney or proteinuria. Interestingly, the combination of pravastatin and imidapril, an angiotensin-converting enzyme inhibitor, had a synergistic effect with (more pronounced) beneficial effects on renal pathology than either of the monotherapies.

Although various animal models have recently been generated that display lupus-enhanced atherogenesis, the effect of statin therapy on the atherosclerotic process has thus far only been evaluated in apoE^{-/-} mice with either an inactivating mutation in Fas ligand (*gld/gld*)¹⁵ or Fas (*lpr/lpr*).¹⁶ In *gld* mice on a C57BL/6 background daily treatment with simvastatin (0.125 mg/kg/day) had no effect on antinuclear antibody titres, splenomegaly, lymphadenopathy or the apoptotic cell accumulation in lymph nodes.¹⁵ Interestingly, crossing of *gld* with apoE^{-/-} mice results in increased lymphadenopathy, splenomegaly and autoimmune antibodies. In addition, *gld*. apoE^{-/-} mice also display immune-mediated glomerular injury which does not occur in *gld* mice. In *gld*.apoE^{-/-} mice, contrary to *gld* mice, simvastatin treatment was shown to significantly reduce antinuclear antibody titres, splenomegaly, submandibular lymph node size as well as renal disease. Also, in *gld*. apoE^{-/-} mice, simvastatin treatment induced a 25% decrease in atherosclerotic lesion size without affecting serum cholesterol levels. These findings are in conflict with a recent study

evaluating pravastatin and L4-F (an apoAI mimetic peptide) in apoE^{-/-} Fas^{-/-} mice.¹⁶ Pravastatin treatment appeared to reduce cellular infiltration of the glomeruli but had no effect on serum IgG anti-dsDNA, spleen size, lymph nodes size or parameters of renal disease. Surprisingly, pravastatin appeared to increase the lesion burden in apoE^{-/-} Fas^{-/-} mice. No differences could be detected in plaque phenotype between untreated and pravastatin-treated mice.

In summary, the currently available animal studies evaluating the effect of statins on lupus activity and lupus-mediated atherogenesis use different animal models, statins, dosages, diets, study duration, study parameters and demonstrate opposite effects. Therefore, there is still much to be learnt from these animal models and additional studies using various treatments in combination with statins are warranted.

Effect of statin therapy on lupus activity in patients with SLE

Only a limited number of studies have evaluated the effect of statin therapy in patients with SLE. In the first pilot study, three patients with SLE (mean erythrocyte sedimentation rate 24 mm/h) with severe renal disease refractory to treatment (prednisone plus cyclophosphamide and azathioprine or methotrexate) were treated with 80 mg of simvastatin daily for a period of 8 days without modification of previous treatments.¹⁷ Surprisingly, simvastatin induced a significant reduction in proteinuria, urine casts, erythrocyturia and leucocyturia, and also diminished expression of CD69 by lymphocytes. Consistent with this, treatment of eight female lupus patients (mean SLE disease activity index (SLEDAI) 14.6) with 20 mg of simvastatin/day for a period of 4 weeks resulted in a significant reduction of serum tumour necrosis factor α levels.¹⁸ As a result of these hopeful cases, Costenbader *et al*²⁰ set out to determine the dose effectiveness and tolerability of statin therapy in patients with SLE. In a dose-escalating study, 41 patients with SLE (mean SLEDAI 7.4) were treated for 1 month with pravastatin 10 mg, followed by a daily dose of 40 mg. Although pravastatin had beneficial effects on lipid levels to the same degree observed in non-SLE patients, an unexpectedly high number of dropouts (17/41 patients) was reported. In only three cases, however, was this directly related to statin side effects. Pravastatin did not affect SLEDAI or C-reactive protein levels in this study. Similarly, no beneficial effects of statin therapy on lupus pathophysiology were observed in a recent study evaluating the effects of a 3-month course of 10 mg/day of rosuvastatin. In 19 patients with SLE with stable, chronic disease (mean C-reactive protein 5.2 mg/l) rosuvastatin treatment induced a potent lipid-lowering effect but did not reduce SLEDAI, proteinuria or a variety of circulating activation markers of inflammation and complement.²¹

Effect of statin therapy on atherogenesis in patients with SLE

Ferreira *et al*²² were the first to assess the effect of statin therapy on a parameter of cardiovascular risk in SLE in addition to lipid levels. They evaluated the effect of statins on a surrogate marker for atherosclerotic vascular disease, endothelial function. Endothelial dysfunction precedes the onset of atherosclerotic lesion formation and various groups have demonstrated endothelial dysfunction in patients with SLE.²⁴ In the study by Ferreira *et al*, 20 mg/day of atorvastatin for 8 weeks in a group of 64 patients with SLE (mean SLEDAI 4.4) significantly improved endothelial function. Of note, endothelial function improved similarly in patients with and without dyslipidaemia present at baseline.²³ This is in line with a similar study demonstrating a beneficial effect on endothelial function of 12-months' treatment with 40 mg pravastatin combined with 10 mg ezetimibe in a group of 22 patients with SLE.²⁵

Unfortunately, an attempt to carry out a randomised controlled trial (RCT) evaluating the antiatherosclerotic effect of pravastatin in SLE (Prevention of Accelerated Atherosclerosis

in SLE Study)²⁶ was discontinued. The study had six treatment arms aiming to assess the atheroprotective potential of pravastatin, aspirin, ramipril and vitamin supplementation. In total, 45% of identified patients were ineligible owing to a medical contraindication to one of the study drugs and another 22% dropped out owing to a potential side effect of one of the study drugs.

Two other RCTs analysing the effect of statin therapy on surrogate markers for atherosclerotic vascular disease in SLE have been completed. Finished in 2006, the Lupus Atherosclerosis Prevention Study (LAPS)²⁷ compared the antiatherosclerotic efficacy of a 2-year treatment period with atorvastatin 40 mg to placebo in 200 patients with SLE. Progression of atherosclerosis was assessed by helical CT (coronary calcification) and carotid duplex (carotid intima-media thickness (cIMT)). Preliminary analyses indicated that atorvastatin significantly attenuated progression of atherosclerosis as assessed by cIMT. As expected, no reversal of coronary calcification was seen. In fact, recent studies have shown that the increase in coronary calcification following statin therapy may represent lesion stabilisation, thereby limiting the use of coronary calcification as a suitable surrogate target in prospective cardiovascular prevention trials.²⁸

The APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) trial is a 3-year, multicentre RCT using cIMT to determine the efficacy and safety of atorvastatin (10 or 20 mg) in preventing the progression of atherosclerosis, in children and adolescents (10–21 years of age) with SLE. In total, 221 participants were enrolled during the inclusion period which was finalised in 2006; study results are expected in 2010.²⁹

Finally, the ability of fluvastatin to reduce major cardiac events was evaluated in kidney transplant recipients with SLE. The ALERT (Assessment of Lescol in Renal Transplantation trial) is a RCT of the effect of fluvastatin on cardiovascular outcomes in renal transplant recipients. In a post hoc analysis, 33 patients with SLE were identified, of whom 23 were randomised to fluvastatin.³⁰ In these 23 fluvastatin-treated patients there was a robust 73.4% reduction in the frequency of major cardiac events compared with 10 patients receiving placebo. It should be noted, however, that the numbers of patients and major cardiac events in this analysis are low and that (end stage) renal disease itself constitutes a major risk factor for CVD.

CONCLUSIONS

- ▶ CVD is a major source of morbidity and mortality in patients with SLE.
- ▶ Although they have not been extensively tested in SLE, statins have a very beneficial risk/benefit profile in cardiovascular risk management in numerous non-SLE populations.
- ▶ In addition to lowering cholesterol, statins have been shown to have immunomodulatory properties, which may be of particular interest in SLE.
- ▶ Making the decision whether or not to initiate statin therapy in SLE dependent on the 10-year cardiovascular risk estimate exceeding 10–20%, does not take lupus into account as a risk factor and will result in undertreatment.
- ▶ Several animal studies using different study protocols have evaluated the effect of statins on lupus activity and lupus-mediated atherogenesis and have demonstrated opposite effects (table 1).
- ▶ A few statin studies have been performed in patients with SLE and while the results for the potential to diminish lupus activity are equivocal, a limited

number of studies show that statins mediate beneficial effects on surrogate markers for atherosclerotic disease in patients with SLE (table 2).

- ▶ RCTs for cardiovascular prevention in patients with SLE have proved to be a challenge and a study of primary prevention of cardiovascular end points will require treating thousands of patients for several years and may not be feasible.
- ▶ Data on the safety and efficacy of statins in SLE from the LAPS and APPLE trials are eagerly awaited.
- ▶ Statin treatment should be considered more often in patients with SLE, even more so in the presence of concomitant risk factors for CVD.

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Table 1

The effect of statin therapy on the development of lupus in different murine models

Authors	Animal model	Diet	Age	Treatment	Duration	Antibody production	Renal disease	Immune system
Lawman <i>et al</i> ¹²	NZB/NZW F ₁ ♀ mice	Not specified	4 Months	Atorvastatin 30 mg/kg/day intrapertitoneal	14 Weeks	*IgG anti-DNA Ab↓ *Total IgG→	*Proteinuria and serum urea↓ *Glomerular hypercellularity and interstitial infiltrates↓ *Smaller increase in glomerular matrix *Glomerular Ig deposition↓	*Expression of MHC-II on splenic B cells and monocytes↓ *MHC-II expression in renal glomeruli↓ *Expression of CD80 and CD86 on B cells↓ *Expression of CD28 on CD4 T cells↓ *Serum TNF→ and IL-4↑
Graham <i>et al</i> ¹³	NZB/NZW ♀ mice	Not specified	20 Weeks	Atorvastatin 10 mg/kg/day oral	20 Weeks	*Anti-dsDNA Abs→	*Proteinuria→ *Slight trend toward reduced glomerular involvement	
Shimazu <i>et al</i> ¹⁴	MRL-Fas ^{pr} ♀ mice	Chow diet	2 Months	Pravastatin 100 mg/kg 3 times per week intrapertitoneal	5 Months	*IgG anti-DNA Ab↓	*Proteinuria→ *Glomerular damage→ *Tubular damage→ *Periglomerular macrophages→ *Periglomerular T cells→ *Glomerular IgG deposition→	*Renal mRNA expression of MCP-1→, IFNγ→ and IL-4→
Arahamian <i>et al</i> ¹⁵	MRL-Fas ^{pr} ♀ mice	Chow diet	2 Months	Pravastatin 100 mg/kg + imidapril 5 mg/kg 3 times per week intrapertitoneal	5 Months	*IgG anti-DNA Ab↓	*Proteinuria↓ *Glomerular damage↓ *Tubular damage↓ *Periglomerular macrophages↓ *Periglomerular T cells→ *Glomerular IgG deposition↓	*Renal mRNA expression of MCP-1↓, IFNγ→ and IL-4↓
Arahamian <i>et al</i> ¹⁵	Gld mice	Western diet	7 Weeks	Simvastatin 0.125 mg/kg/day intrapertitoneal	12 Weeks	*ANA→	*No pathological renal phenotype; no effect of simvastatin	*Submandibular lymph node size→ *Apoptotic cell accumulation in lymph nodes→ *Splenomegaly→
	Gld.apoE ^{-/-} mice	Western diet	7 Weeks	Simvastatin 0.125 mg/kg/day intrapertitoneal	12 Weeks	*ANAV	*Proteinuria↓ *Glomerular tuft volume↓	*Submandibular lymph node size↓ *Apoptotic cell accumulation in lymph nodes↓ *Splenomegaly↓ *Serum TNFα and IFNγ↓ *IL-4 and IL-10 mRNA↑
Woo <i>et al</i> ¹⁶	ApoE ^{-/-} Fas ^{-/-} ♀ mice	Chow diet	8-9 Weeks	Pravastatin 5 mg/kg/day oral	27 Weeks	*Total IgG→ *IgG anti-dsDNA Ab→ *IgG anti-oxPLs→	*Proteinuria→ *Glomerular cell infiltration↓ *Glomerular tuft size→	*Size lymph nodes→ *Spleen size→ *B cells, CD4 and CD8 T cells, NK, CD11c and CD11b→ *Plasma IL-10→, CCL9→, VCAM-1→ and CCL19→
	ApoE ^{-/-} Fas ^{-/-} ♀ mice	Chow diet	8-9 Weeks	Pravastatin 5 mg/kg/day oral + L-4F 15 mg/	27 Weeks	*Total IgG→ *IgG anti-DNA Ab→ *IgG anti-oxPLs↓	*Proteinuria→ *Glomerular cell infiltration↓ *Glomerular tuft size↓	*Size lymph nodes↓ *Spleen size→ *Splenic B cells, CD4 and CD8 T

Authors	Animal model	Diet	Age	Treatment	Duration	Antibody production	Renal disease	Immune system
				kg 5 days/week intraperitoneal				cells, NK, CD11c and CD11b→ *Plasma IL-10→, CCL9→, VCAM-1→ and CCL19↓

* All outcome measures are relative to mice not receiving treatment.

Ab, antibody; ANA, antinuclear antibody; IFN γ , interferon γ ; IL, interleukin; MCP, monocyte chemoattractant protein; MHC, major histocompatibility complex; oxPLs, oxidised phospholipids; TNF α , tumour necrosis factor α ; VCAM, vascular cell adhesion molecule.

Table 2

Effect of statin therapy in patients with SLE

Authors	SLE population	Disease activity	Treatment	Duration	Outcome
Abud-Mendoza <i>et al</i> ¹⁷	Three patients with refractory renal disease, mean age 37.7 years	SLEDAI NS ESR 24 mm/h Proteinuria 5.0 g/l	Simvastatin 80 mg/day	8 Days	*Proteinuria levels↓ *Urine casts, erythrocyturia and leucocyturia↓ *CD69 expression by lymphocytes↓ *Spontaneous apoptosis of lymphocytes↓ *Expression of HLA-DR by monocytes↓
Koyla <i>et al</i> ¹⁸¹⁹	Eight female patients, mean age 42 years, mean disease duration 22.8 months	SLEDAI 14.6	Simvastatin 20 mg/day	28 Days	*Flow-mediated dilatation↑ *Serum TNFα↓ *TC↓, LDL↓, HDL→, TG→
Costenbader <i>et al</i> ²⁰	41 (38♀/3♂) Patients, mean age 47.9 years, mean disease duration 12.7 years	SLEDAI 7.4	Pravastatin 10 mg/day	1 Month	*SLEDAI→ *CRP→ *TC↓, LDL↓, HDL↓, TG→
de Kruif <i>et al</i> ²¹	19 Patients with stable, chronic disease	SLEDAI NS CRP 5.2 mg/l	Rosuvastatin 10 mg/day	3 Months	*CRP, ESR, SLEDAI, dsDNA antibodies, 24 h urine protein, 24 h microalbumin and creatinine clearance→ *C1q, C3, C4, IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNFα→ TC↓, LDL↓, apoB↓, HDL→, apoAI→, TG→, Lp(a)→
Ferreira <i>et al</i> ²²²³	64 Female patients with SLE, mean age 32 years, mean disease duration 8.5 years	SLEDAI 4.4 SLICC 1.1	Atorvastatin 20 mg/day	8 Weeks	*Flow-mediated dilatation↑ *SLEDAI↓ *Plasma CCL2→, CCL3→, CXCL9↓ *TC↓, LDL↓, HDL→, TG↓
Vera-Lastra <i>et al</i> ²⁵	22 (31♀/1♂) Patients, mean age 40 years	SLEDAI NS	Pravastatin 40 mg/day + Ezetimibe 10 mg/day	12 Months	*Flow-mediated dilatation↑ *CRP↓ *TC↓, LDL↓ HDL↑
Norby <i>et al</i> ³⁰	23 Patients who underwent kidney transplantation, mean age 46.4 years	SLEDAI NS hsCRP 3.4 mg/l	Fluvastatin 40–80 mg/day	7–8 Years	*TC↓, LDL↓, HDL→, TG↓ *Risk of major cardiac events↓

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; MHC-II, major histocompatibility complex class II; NS, not specific; NZB/NZW, New Zealand black/white; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; SLICC, Systemic Lupus International Collaborating Clinics; TC, total cholesterol; TG, triglycerides; TNFα, tumour necrosis factor α.