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Effect of Fluvastatin on Cardiac Outcomes in Kidney Transplant Patients With Systemic Lupus Erythematosus

A Randomized Placebo-Controlled Study

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Objective. **Patients with systemic lupus erythematosus (SLE), with or without end-stage renal failure, are at increased risk of premature cardiovascular disease. Although statin therapy has been found to reduce cardiovascular risk in the general population, its effectiveness in kidney transplant recipients with SLE has not been examined. This study was undertaken to investigate the effect of fluvastatin on cardiac end points in a randomized controlled trial of renal transplant patients with SLE.**

Methods. **Patients with SLE were identified from among participants in the Assessment of Lescol in Renal Transplantation trial, a randomized, double-blind, placebo-controlled study of the effect of fluvastatin (40–80 mg/day) on cardiovascular outcomes in renal transplant recipients. Patients were randomized to either a group receiving fluvastatin or a placebo group for the duration of the 5–6-year trial, and then invited to continue in a 2-year open-label extension during which all participants, regardless of original group, received fluvastatin. Patients were followed up for a total of 7–8 years for assessment of the primary end point of major cardiac events, comprising nonfatal myocardial infarction, cardiac death, and coronary intervention procedures.**

Results. **Fluvastatin reduced low-density lipoprotein cholesterol levels by 29.2% (95% confidence interval [95% CI] 18.3–40%), from a mean ± SD of 4.0 ± 0.9 mmoles/liter to 2.8 ± 1.1 mmoles/liter, and total cholesterol by 19.6% (95% CI 11.7–27.5%), from 6.4 ± 0.9 mmoles/liter to 5.1 ± 1.1 mmoles/liter. Compared with placebo-treated patients, patients randomized to receive fluvastatin exhibited a 73.4% reduction in the risk of major cardiac events (relative risk 26.6 [95% CI 5.9–119.4], $P = 0.064$).**

Conclusion. **Our results indicate that the effect of fluvastatin on cardiac events in renal transplant recipients with SLE is similar to that observed with statin therapy in the renal transplant population as a whole.**

Systemic lupus erythematosus (SLE) predominantly affects young women during their childbearing years, and premature coronary heart disease (CHD) is a major cause of morbidity and mortality in this population (1). Lupus nephritis is a common manifestation of SLE; 50–60% of SLE patients will develop some kind of renal involvement, with 10–15% of these cases progress-

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ing to end-stage renal disease (ESRD) (2). Renal transplantation, the preferred treatment option for SLE patients with ESRD (3), is associated with an increased risk of premature cardiac disease and death in SLE patients compared with the general population (4), compounding the already heightened risk of CHD in patients with SLE.

The Assessment of Lescol in Renal Transplantation (ALERT) study is the largest randomized placebo-controlled trial of lipid-lowering therapy undertaken in renal transplant recipients (2). In that study, 2,102 renal transplant patients were allocated to groups receiving either placebo or fluvastatin (40–80 mg/day), with a total followup of 7–8 years. Compared with patients randomized to the placebo group, patients taking fluvastatin experienced a 21% reduction in the risk of major adverse cardiac events and a 29% reduction in the risk of cardiac death or nonfatal myocardial infarction (2). However, although statin therapy reduces cardiovascular risk during the posttransplantation period overall, cardiac risk profiles vary according to the original disease leading to end-stage renal failure. The most notable example is diabetes mellitus (DM), but renal transplant patients with SLE may also be at increased risk, due to an accumulation of risk factors.

Conventional risk factors for CHD in SLE patients are hypertension, DM, dyslipidemia, and obesity; nonconventional risk factors include premature menopause and chronic renal impairment, as well as specific "lupus factors," such as chronic inflammation and antiphospholipid antibodies (1). In other reports, different specific CHD risk factors in SLE patients have been claimed to be the most important to address, but strategies for combating cardiovascular disease in this population are typically based on consensus statements (5–7). There has also been a worrisome lack of randomized controlled trials focused on this population. Although statin therapy has been shown to reduce the risk of cardiovascular disease in diverse populations, its efficacy and safety in SLE patients in general, and in renal transplant recipients with SLE in particular, have not been established. Herein, we report the results of an investigation into the effect of statin therapy in a subpopulation of kidney transplant patients with SLE who took part in the large-scale ALERT study.

PATIENTS AND METHODS

The ALERT study design and findings have been described in detail previously (4). Briefly, the ALERT study was a randomized, double-blind, placebo-controlled study conducted in 2,102 adult renal transplant recipients recruited from nephrology and transplant clinics in northern Europe and Canada. Patients had received a kidney transplant >6 months prior to randomization and were enrolled if the total fasting cholesterol level was 4–9 mmoles/liter (4–7 mmoles/liter for patients with a previous cardiac event). The ALERT study was designed and coordinated by an investigator-led, independent steering committee, and all end points, including CHD end points, were adjudicated by an independent critical event committee.

Patients were initially randomized to either a group receiving fluvastatin (40 mg/day) or a group receiving matching placebo. Because of emerging data on fluvastatin and data from other cardiac outcome trials, the dosage of fluvastatin and placebo was doubled after ~2 years. Upon completion of the study, all patients were invited to take part in a 2-year open-label extension in which they received fluvastatin (80 mg extended release) once a day, regardless of original randomized grouping. Two patients were withdrawn from the fluvastatin group due to noncompliance, after 1.2 and 2.6 years. All other patients continued to receive the study drug (fluvastatin for the duration of the trial, or placebo followed by 2 years of fluvastatin) for the entire followup time of 7–8 years.

Study visits took place at 1.5 months after randomization and at 6-month intervals thereafter. At each visit, clinical status was assessed. Lipid, serum creatinine, creatine kinase, and hepatic enzyme levels were measured at a central laboratory (CRL.Medinet, Breda, The Netherlands). The study adhered to the International Conference on Harmonisation Guidelines for Good Clinical Practice and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent, and the institutional review board at each participating center approved the trial.

For the purposes of our investigation, ALERT study participants with SLE were identified (SLE was diagnosed if a patient met 4 of the 11 criteria specified by the American College of Rheumatology [8]). In most centers, a renal biopsy was also required to verify the diagnosis lupus nephritis.

A post hoc analysis of the SLE patients was performed to evaluate the incidence of major cardiac events, defined as cardiac death, nonfatal myocardial infarction, and coronary intervention procedures. A log rank test was used to assess the differences in time to the first major cardiac event. Cumulative incidence curves were generated by the Kaplan-Meier method. The Cox proportional hazards model was used to assess risk reduction.

RESULTS

Thirty-three renal transplant recipients with SLE were identified. In these patients, transplantation had occurred a mean of 4.5 years prior to study randomization, and the graft was functioning well in all cases. The mean age at transplantation was 41.4 years (~10 years younger than that of the total ALERT study population). Compared with the total population, the SLE patient group also had a higher proportion of women and a higher proportion of patients who had received immunosuppressive drugs before transplantation (because of lupus nephritis). Of the 33 SLE patients iden-

Table 1. Baseline clinical characteristics of the SLE patients randomized to receive placebo or fluvastatin in the ALERT study*

	Placebo (n = 10)	Fluvastatin (n = 23)
Age, years	47.1 ± 11.2	46.4 ± 9.2
BMI, kg/m^2	26.7 ± 5.1	26.3 ± 5.2
Blood pressure, mm Hg		
Systolic	111.6 ± 27.1	120.4 ± 33.0
Diastolic	85.7 ± 8.7	88.2 ± 8.6
Lipids, mmoles/liter		
Total cholesterol	6.2 ± 1.2	6.4 ± 0.9
LDL cholesterol	3.9 ± 1.1	4.0 ± 0.9
HDL cholesterol	1.3 ± 0.4	1.4 ± 0.5
Non-HDL cholesterol	4.8 ± 1.2	4.9 ± 1.1
Triglycerides	1.9 ± 0.4	2.2 ± 1.2
Apolipoprotein B, mg/dl	111.6 ± 27.1	120.4 ± 33.0
Creatinine, μmoles/liter	129.4 ± 67.4	133.5 ± 62.7
Glucose, mmoles/liter	3.9 ± 0.5	4.1 ± 0.7
Calcium, mmoles/liter	2.4 ± 0.1	2.5 ± 0.2
Phosphate, mmoles/liter	1.3 ± 0.4	1.2 ± 0.2
hsCRP, mg/liter	2.7 ± 2.9	3.4 ± 6.9
Interleukin-6, pg/ml	2.6 ± 1.4	2.8 ± 2.0

* Values are the mean ± SD. SLE = systemic lupus erythematosus; ALERT = Assessment of Lescol in Renal Transplantation; BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein.

tified, 23 had been randomized to the group given fluvastatin and 10 to the placebo group. Baseline characteristics were similar in the 2 groups (Table 1), and mean followup in the 2 groups combined was 7.3 years.

All SLE patients were receiving immunosuppressive treatment with cyclosporine, with the majority also receiving azathioprine and corticosteroids. Approximately 70% of the patients in each treatment arm were

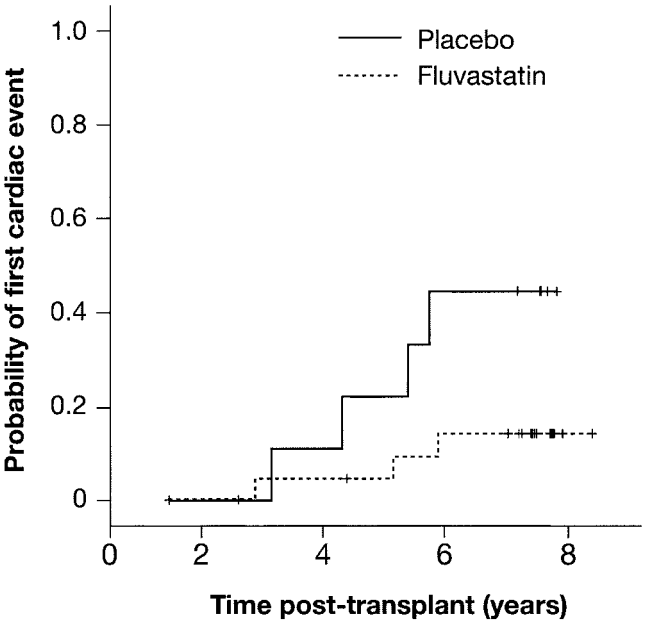

Figure 1. Kaplan-Meier estimates of the time to first cardiac event in the placebo and fluvastatin treatment arms.

Table 2. Number of patients with notable increases in levels of parameters used to assess fluvastatin safety*

	Placebo (n = 10)	Fluvastatin (n = 23)
ALT 1.5–2× ULN	2	2
ALT >2× ULN	0	0
AST 1.5–2× ULN	1	1
AST >2× ULN	0	0
CK >2× ULN	0	0

* ALT = alanine aminotransferase (normal 0–45 IU/liter); ULN = upper limit of normal; AST = aspartate aminotransferase (normal 0–45 IU/liter); CK = creatine kinase (normal 35–232 IU/liter).

treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker medication. There were no significant differences between the fluvastatin and placebo groups in terms of frequency of treatment with any comedication.

The SLE patients included in our study had elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (Table 1), all of which were similar to the levels found in the total ALERT population. Also, concentrations of the inflammation markers high-sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6) in the SLE patients did not differ from the values observed in the total population. The baseline values of CRP and IL-6 in the core ALERT trial were a mean ± SD of 3.8 ± 6.7 mg/liter (n = 1,910) and 2.9 ± 1.9 pg/ml (n = 1,751), respectively.

Fluvastatin reduced LDL cholesterol levels by 29.2% (95% confidence interval [95% CI] 18.3–40.0%), from a mean ± SD of 4.0 ± 0.9 mmoles/liter to 2.8 ± 1.1 mmoles/liter, and total cholesterol by 19.6% (95% CI 11.7–27.5%), from 6.4 ± 0.9 mmoles/liter to 5.1 ± 1.1 mmoles/liter. No significant effect of fluvastatin on high-density lipoprotein cholesterol or triglyceride levels was observed.

Of the SLE patients in the placebo group, 4 of 10 (40.0%) experienced a cardiac event during followup, compared with 3 of 23 in the fluvastatin group (13.0%). Thus, fluvastatin therapy was associated with a 73.4% reduction in the frequency of major cardiac events, which was numerically marked but of borderline statistical significance (relative risk 26.6 [95% CI 5.9–119.4], $P = 0.064$). Kaplan-Meier estimates of the time to first cardiac event in each treatment group are shown in Figure 1.

Safety was assessed based on measurements of hepatic enzyme and creatine kinase levels. These measurements revealed no safety concern with the use of

fluvastatin in kidney transplant patients with SLE (Table 2).

DISCUSSION

Our analysis has shown that fluvastatin therapy in kidney transplant patients with SLE may be associated with a reduction of major cardiac events, with no apparent safety concerns. The effect of fluvastatin observed in this population was similar to the overall results of the ALERT study and of studies using statin treatment in other settings (9). In the ALERT trial, the occurrence of major cardiac events was reduced by 21% among patients randomized to receive fluvastatin compared with those receiving placebo (2). The percentage risk reduction associated with fluvastatin in the SLE subpopulation investigated in the present study was substantially higher numerically than in the total ALERT population, but in view of the small patient population in our study, a conservative interpretation is that the effect of fluvastatin in SLE patients mirrors that seen in the entire cohort of ALERT participants.

No placebo-controlled trials of lipid-lowering therapy with well-defined cardiovascular end points have been undertaken in SLE patients. There also appears to be a barrier to recruiting SLE patients into randomized trials; one study had to be discontinued because of recruitment and retention difficulties (10). However, a few trials involving SLE patients have been performed using surrogate markers for cardiovascular end points. One study investigated the effect of atorvastatin on the prevention of atherosclerosis among 200 SLE patients in a 2-year, randomized, double-blind, placebo-controlled trial (11). Findings of the study indicated that atorvastatin at 40 mg/day may be superior to placebo in slowing the progression of carotid intima-media thickness, but no effect on coronary calcium progression or disease activity was observed. However, the available data from that study are preliminary and have been presented only in abstract form; a full report is awaited. In a short-term study of patients with SLE, atorvastatin improved endothelium-dependent vasodilatation independently of the presence of conventional risk factors (12), indicating that atorvastatin may be useful in preventing atherosclerotic cardiovascular complications in this clinical setting.

Atherosclerosis Prevention in Pediatric Lupus Erythematosus is an ongoing randomized controlled study that will test the efficacy of statins in preventing premature atherosclerosis in children and adolescents with SLE (13). In another current study, SLE patients have been randomized to participate in a multiple-intervention program for cardiovascular disease reduction versus usual care (14). Preliminary data from that study indicate some benefits of the multiple-intervention program in reducing the estimated 8-year cardiovascular risk, but no cardiovascular end points have been reported.

Several reports describe a range of "independent" risk factors for cardiovascular events in patients with SLE (15). The search for additional risk factors is based on the fact that the risk factor formula from the Framingham study cannot fully explain the increased risk for cardiovascular events seen in SLE patients (16). The nonconventional risk factors proposed include prednisolone use, markers of inflammation, and the disease itself, with various disease activity markers (15). However, results of 2 well-conducted, randomized controlled trials have cast doubt on whether there is an association between cardiovascular risk and either clinical and serologic measures of disease activity or serum levels of CRP in SLE (5,6).

Outcomes following kidney transplantation in SLE patients are uncertain, with some studies showing patient and graft survival rates below those rates found among non-SLE recipients, and others demonstrating comparable survival rates (2). However, SLE patients who undergo renal transplantation are different from non-SLE transplant patients in many respects. Transplant patients with SLE are generally younger, and the majority are women. In addition, cardiovascular disease occurs more frequently in patients with lupus nephritis and contributes to increased mortality and morbidity posttransplantation. Although some reports describe similar survival rates among patients with or those without SLE, they fail to acknowledge that SLE patients are generally younger at transplantation. Thus, even if the patient survival time is not numerically different, the age at death is. SLE patients have an accumulation of cardiovascular risk factors which continue to be present after transplantation. Although kidney transplantation is the preferred intervention for SLE patients with end-stage renal failure, it does not necessarily supersede all pretransplant cardiac risk factors.

The potential side effects of statin therapy on the liver and muscles of patients with SLE are a concern for rheumatologists, although there is no substantial documentation of such problems. Costenbader and colleagues performed a dose-escalation study with pravastatin in 41 SLE patients and observed a mild rise in the creatine kinase level in 1 patient (17). In general, side effect profiles in statin trials have not demonstrated any difference between placebo and treatment groups (9). The SLE patients randomized to receive fluvastatin in

the ALERT trial did not experience any increase in liver or muscle enzyme levels compared with the placebo group.

Our study had several limitations. Patient numbers were low, and few major cardiac events occurred. Also, the difference in risk of major cardiac events between patients receiving fluvastatin and those receiving placebo was statistically borderline. However, recruitment of large numbers of SLE patients is always difficult, and while the small population size is problematic from both a statistical and a clinical point of view, it should not be a barrier to utilizing available data from small disease populations. The strengths of the trial were the long followup, the randomized, controlled, blinded design, and the independent adjudication of major cardiac end points.

In conclusion, results from this placebo-controlled trial of lipid-lowering therapy show a cardiovascular benefit in kidney transplant recipients with SLE, although the small patient numbers need to be taken into account. The effect of fluvastatin on cardiac events was similar to that observed with statin therapy in other populations, and statin therapy should be considered for SLE patients following kidney transplantation. Whether differences exist between this subpopulation of SLE patients and the SLE population as a whole is not known and needs to be examined in future studies.

AUTHOR CONTRIBUTIONS

Dr. Norby 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 design. Fellström, Jardine, Cole, Holdaas.

Acquisition of data. Norby, Fellström, Jardine, Cole, Abedini, Holdaas.

Analysis and interpretation of data. Norby, Holme, Fellström, Jardine, Cole, Abedini, Holdaas.

Manuscript preparation. Norby, Fellström, Jardine, Cole, Abedini, Holdaas.

Statistical analysis. Norby, Holme, Fellström, Jardine, Cole, Abedini, Holdaas.

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