EXTENDED REPORT

Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXIV. Cytotoxic treatment is an additional risk factor for the development of symptomatic osteonecrosis in lupus patients: results of a nested matched case-control study

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Ann Rheum Dis 2006;**65**:785–790. doi: 10.1136/ard.2005.040428

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Accepted 23 October 2005
Published Online First
3 November 2005

Background: Osteonecrosis is common in systemic lupus erythematosus (SLE) and often disabling. The role of glucocorticoids in its development is well known.

Objective: To explore other possible risk factors for osteonecrosis in SLE.

Methods: A nested matched case-control study undertaken in the context of a large, longitudinal, multiethnic lupus cohort (LUMINA), currently formed of 571 SLE patients meeting American College of Rheumatology criteria. All those developing symptomatic osteonecrosis after the diagnosis of SLE were considered cases. Two controls matched for age, disease duration, ethnicity, and centre were selected for each case. Cases and controls were compared by univariable analyses using selected variables. Variables with $p < 0.10$ and those thought clinically relevant were entered into conditional logistic regression models including either the average dose or the highest dose of glucocorticoids, with osteonecrosis as the dependent variable.

Results: 32 cases were identified and 59 matched controls selected (in five cases only one control could be found). By univariable analyses, both groups were largely comparable for socioeconomic-demographic, clinical, and laboratory variables. Cases were less exposed to hydroxychloroquine (as assessed by the percentage of exposure time) ($p = 0.026$), used higher doses of glucocorticoids (average and highest doses) ($p = 0.011$ and 0.001 , respectively), and received cytotoxic drugs more often ($p = 0.015$). In the multivariable analyses only cytotoxic drug use (both models) and the highest dose of glucocorticoids remained associated with the occurrence of osteonecrosis.

Conclusions: Cytotoxic drug use is a risk factor for the development of symptomatic osteonecrosis in SLE patients, along with glucocorticoids. No definite protective factors were identified.

Osteonecrosis is a relatively frequent and disabling complication occurring in patients with systemic lupus erythematosus (SLE), often requiring major surgical procedures as treatment. It has been reported to occur in 40% of patients if silent cases are included, and approximately 15% of patients develop symptomatic osteonecrosis.^{1–9} Glucocorticoid use is considered a risk factor for the occurrence of osteonecrosis in general, but particularly in patients with SLE.^{10–11} Other factors may also be implicated in its development, as osteonecrosis has been described in SLE patients who have not received glucocorticoids.¹¹ Additional risk factors have been variably identified by different investigators^{9–12–16}; these include a Cushingoid body habitus, smoking, thrombophlebitis, vasculitis, Raynaud's phenomenon, arthritis, presence of certain autoantibodies (anti-phospholipid (aPL), anti-Ro plus anti-RNP, or anti-topoisomerase I), or disease related fibrinolytic abnormalities. In none of these studies, however, has an attempt been made to identify possible protective factors for the occurrence of this complication in patients with SLE.

We thus undertook a study examining both possible risk factors and possible protective factors in the development of symptomatic osteonecrosis in SLE, using a nested matched case-control design in the context of a large multiethnic longitudinal lupus cohort.

METHODS

Patients

As previously described,^{17–18} LUMINA (LUPus in MInority populations: NAture v Nurture) is a longitudinal study of outcome in SLE and includes patients from three ethnic groups living in the USA: Hispanics from Texas and Puerto Rico, African Americans, and whites; when this study was conducted the cohort comprised 571 patients. LUMINA is being conducted in three geographical areas (Alabama, Texas, and the island of Puerto Rico) and at three institutions: the University of Alabama at Birmingham, the University of Texas Health Science Center at Houston¹, and The University of Puerto Rico Medical Sciences Campus. Patients with SLE according to the American College of Rheumatology (ACR) criteria,^{19–20} with a disease duration of five years or less, defined ethnicity (all four grandparents of the same ethnic group as the patient), and living in the geographical recruitment areas of the participating institutions are eligible to be enrolled in LUMINA. Every patient has

Abbreviations: ACR, American College of Rheumatology; aPL, anti-phospholipid antibodies; LAC, lupus anticoagulant; LUMINA, Lupus in Minorities: Nature v Nurture; NSAID, non-steroidal anti-inflammatory drug; SDI, Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index; SLE, systemic lupus erythematosus

a baseline visit (T0); follow up visits are conducted every six months for the first year (T0.5 and T1, respectively), and yearly thereafter (T2, T3, and so on until TL, the last available visit). At each visit, an interview, a physical examination, and laboratory tests are performed; a review of all previously available medical records is also done to obtain pertinent clinical information for the interval. Data for missed study visits are obtained, whenever possible, by review of medical records.

Disease duration was defined as the time elapsing from the date the patient met four ACR criteria (diagnosis date or TD herein) to T0, whereas duration of follow up in the cohort was defined as the time between T0 and TL (follow up time, herein); therefore total disease duration was defined as the time elapsing from TD to TL.

Variables

As previously reported,^{18,21} the LUMINA database includes variables from the following domains: socioeconomic-demographic, clinical, immunological, immunogenetic, and behavioural and psychological. These variables are measured at T0 and at every subsequent visit. Only the variables included in the present analyses will be described. From the socioeconomic-demographic domain, variables included were ethnicity, age, sex, and unhealthy behaviours (smoking, drinking, and sedentary lifestyle). From the clinical domain, the variables included were disease duration (TD–T0), follow up time (T0–TL), total disease duration time (TD–TL), body mass index, disease activity and disease damage at T0, presence of arthritis and Raynaud's phenomenon, comorbidities, ancillary laboratory tests, and drugs.

Disease activity was assessed using the Systemic Lupus Activity Measure–Revised (SLAM-R).²² Disease damage was assessed using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index or SDI²³; for this study the osteonecrosis item was removed from the SDI score. For patients with disease duration of less than six months at T0, the first SDI score measured (T0.5) was used in the analyses.

Co-morbidities included were diabetes mellitus (self reported and/or physician based diagnosis, and/or requiring pharmacological treatment) and hypertension (defined as a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg on two or more occasions and/or patient self reported intake of antihypertensive drugs, regardless of the cause).

Laboratory variables were obtained at T0. These were non-fasting serum lipoproteins (total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and low density lipoprotein (LDL) cholesterol, calculated using the Friedewald formula), and serum C reactive protein (measured as high sensitivity-CRP (hs-CRP) immunometric assay, Immulite 2000 Diagnostic Products Corporation, Los Angeles, California, USA).

Autoantibodies were measured at T0 and included IgG and IgM aPL antibodies (abnormal >13 GPL U/ml or >13 MPL U/ml, or both) by enzyme linked immunosorbent assay (ELISA)²⁴; lupus anticoagulant (LAC) (Staclot test Diagnostica Stago 92600, Asnières-Sur-Seine, France)^{25,26}; and IgG and/or IgM anti-oxidised LDL (oxLDL) antibodies (for the purpose of this study, "abnormality" was defined as greater than the mean plus one standard deviation of values for 50 unselected healthy individuals) by ELISA (Specialty Laboratories, Santa Monica, California, USA).²⁷ Patients were considered to have aPL antibodies if they had IgM and/or IgG

antiphospholipid antibodies and/or LAC, as described above, or if these antibodies were present between TD and T0, as recorded in the medical records.

Drugs included were the current and past use of non-steroidal anti-inflammatory drugs (NSAIDs), statins, and cytotoxic drugs (cyclophosphamide, either oral or intravenous, or azathioprine or both). Hydroxychloroquine exposure was recorded as current and past use (yes or no), average dose, and percentage time of exposure over the total disease duration (from TD to TL). TL for cases was defined as the time at which the event (osteonecrosis) occurred; TL for the controls was a time comparable to the time of the event for the matched case. Glucocorticoid use was recorded as the average daily dose of prednisone and as the highest dose ever taken from TD to TL. Exposure to these drugs between TD to T0, which had not been recorded in detail at T0 and thus not included in the original LUMINA database, were completed by review of all available medical records.

Outcome variable

Osteonecrosis events included were those ascertained by the study physician during LUMINA study visits or documented in the medical records reviewed for these visits, or both; thus they were symptomatic. The diagnosis of osteonecrosis was made by the treating rheumatologists using standard procedures (plain radiographs or magnetic resonance images or both) during regular clinic visits. All patients with at least one osteonecrosis event documented after TD were defined as cases.

Patients

We identified 33 cases of osteonecrosis in our cohort; one case was excluded, as the diagnosis of osteonecrosis had been made before the diagnosis of SLE. From the LUMINA database two controls for each patient matched by age (± 5 years), sex, ethnicity, disease duration (± 5 months), and study centre were identified.

Table 1 Selected baseline (T0)* socioeconomic-demographic and clinical features in cases and controls

Variable	Cases (n = 32)	Controls (n = 59)	p Value†
Ethnicity			
Hispanic Texas	22%	22%	
Hispanic Puerto Rico	3%	2%	
African American	56%	57%	
White	19%	19%	
Age (years)	32.2 (10.9)	37.1 (12.4)	0.064
Sex (women)	81%	82%	
Poverty (below)‡	41%	43%	
Body mass index	25.6 (5.3)	26.5 (4.3)	
Drinking alcohol	12%	9%	
Smoking	9%	12%	
Disease duration (months)			
TD–T0	24.8 (16.5)	19.8 (16.4)	
TD–TL (follow up)	21.9 (25.4)	26.5 (28.3)	
TD–TL (total)	46.8 (25.7)	46.2 (27.3)	
Diabetes	12%	7%	
Hypertension	59%	49%	
Arthritis	87%	88%	
Raynaud's phenomenon	34%	37%	
SLAM-R score	9.8 (4.8)	10.0 (4.9)	
SDI score	0.9 (1.3)	1.1 (1.3)	

Values are mean (SD) or per cent.

*Except as noted.

†Only p values ≤ 0.10 are shown.

‡As defined by the US Federal Government, adjusted for the number of household inhabitants.

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLAM, Systemic Lupus Activity Measure–Revised; TD, diagnosis date; TL, last visit date (event for cases and comparable time for controls).

¹ Some patients currently followed at the University of Texas Health Science Center at Houston were originally enrolled at the University of Texas Medical Branch at Galveston.

Table 2 Selected baseline (T0)* laboratory features in cases and controls

Variable	Cases (n = 32)	Controls (n = 59)	p Value†
Cholesterol (mmol/l)			
Total	4.84 (2.06)	4.48 (1.56)	
HDL‡ cholesterol	0.83 (0.39)	0.98 (0.51)	
LDL§ cholesterol	3.41 (2.11)	2.77 (1.30)	0.088
Triglycerides (mmol/l)	1.32 (0.60)	1.46 (0.77)	
IgM anti-oxidised LDL antibodies (U/ml)	30%	36%	
IgG anti-oxidised LDL antibodies (U/ml)	13%	21%	
Any aPL antibody‡	38%	32%	
Lupus anticoagulant	7%	2%	

Values are mean (SD) or per cent.

*Except as noted.

†Only p values ≤ 0.10 are shown.

‡IgG and/or IgM antiphospholipid antibodies and/or the lupus anticoagulant, obtained at T0 or between diagnosis and T0.

aPL, antiphospholipid; HDL, high density lipoprotein; LDL, low density lipoprotein.

Statistical analyses

The dependent variable in all analyses was osteonecrosis. Categorical and continuous variables were examined by χ^2 and Students' *t* tests, respectively; the Fisher's exact test was used when appropriate. Variables with a probability (*p*) value ≤ 0.10 in these analyses, and those thought to be relevant for the study, were examined using conditional logistic regression models with backward selection: in model 1 the average daily dose of glucocorticoids was included; in model 2 the highest dose was included. All analyses were done using SAS version 8.1 (Cary, North Carolina, USA). In all analyses the level of statistical significance was set at *p* ≤ 0.05.

RESULTS

Descriptive analyses

Ninety one patients (74% women; 32 cases and 59 controls) were included in the analyses; for five cases only one control could be selected. Twenty two per cent of the patients were Hispanics from Texas, 2% Hispanics from Puerto Rico, 57% African Americans, and 19% were white. The patients' mean (SD) age at enrolment was 35.0 (12.0) years, and their mean total disease duration (TD to TL) was 46.4 (26.6) months.

Univariable analyses

As showed in table 1 all socioeconomic-demographic and clinical variables examined were, by and large, comparable between the two patient groups; however, controls were older than cases, though the difference did not reach statistical

significance. Selected laboratory findings are given in table 2. Other than LDL-cholesterol levels, which were higher among cases than among controls, no major differences were observed in other lipoproteins; likewise, aPL antibodies and IgG or IgM anti-oxidised LDL antibodies were comparable in cases and controls. LAC was more common in the cases than in the controls (7% *v* 2%), but the difference was not statistically significant.

Exposure to different drugs is shown in table 3. No differences were found with respect to the use of statins and NSAIDs. Cases used hydroxychloroquine less often and had also taken a lower mean dose, but these differences were not statistically significant. The exposure time to hydroxychloroquine was lower among cases than among controls (40% *v* 59%; *p* = 0.026). As expected, cases had been exposed to higher average daily dose of glucocorticoids than controls (22.8 *v* 14.8 mg; *p* < 0.011), and the highest dose received for the first group was also higher than among the second group, at 55.3 *v* 37.6 mg (*p* = 0.001). Cases were also more likely to have been exposed to cytotoxic drugs than controls (59% *v* 32%; *p* = 0.015).

Multivariable analyses

Table 4 shows the results of the multivariable analyses. In each model, both cytotoxic drug use and glucocorticoid use were associated with symptomatic osteonecrosis, although the average daily dose of glucocorticoids was only of borderline significance. The odds ratios (OR) were, for cytotoxic drugs, 3.89 (95% confidence interval, 1.39 to 10.93) (*p* = 0.010), and 3.04 (1.02 to 9.04) (*p* = 0.046); and for glucocorticoid use, 1.03 (0.10 to 1.07) (*p* = 0.085) for average glucocorticoid dose, and 1.03 (1.00 to 1.05) (*p* = 0.027) for the highest dose. No interaction between cytotoxic drug treatment and glucocorticoid use was found when an interaction term was entered into the analyses. A significant negative association between osteonecrosis and serum triglycerides was observed in model 1 (average daily dose of glucocorticoids) (OR = 0.99 (0.98 to 1.00); *p* = 0.046), but this association was only of borderline significance in model 2 (highest dose of glucocorticoids) (OR = 0.99 (0.97 to 1.01); *p* = 0.056).

DISCUSSION

The results of this study confirm the association between the occurrence of symptomatic osteonecrosis and glucocorticoid use in SLE patients. They also show that the use of cytotoxic drugs is an additional risk factor for the occurrence of this complication in SLE patients but failed to identify any protective factor. We did not have an a priori hypothesis about potential protective factors for the development of osteonecrosis, although we had some preliminary data pointing towards antimalarials. However, neither antimalarials nor any other variable examined turned out to be protective against osteonecrosis.

As already mentioned, the association between glucocorticoid use and osteonecrosis in SLE is well known. However, no definitive conclusions have been reached with regard to the specifics of this association, including the route of administration of glucocorticoids, their mean dose, their cumulative dose, or the highest dose used.^{10 11 28} We have now demonstrated that the highest dose appears to be more important than the average daily dose. We also observed an association with the duration of glucocorticoid exposure (data not shown), but this variable was not included in the analyses given that these exact data could not be obtained for all patients. We must add that data on the route of glucocorticoid administration were not recorded in our patients; we believe, however, that in the majority of patients the oral route was used. Our data suggest that exposure to high doses

Table 3 Drug exposure in cases and controls

Variable	Cases (n = 32)	Controls (n = 59)	p Value*
NSAID use	44%	44%	
Hydroxychloroquine use			
Use, ever	69%	76%	
Average dose (mg)	248.0 (180.3)	271.3 (166.1)	
Per cent exposure time	40%	59%	0.026
Statin use	7%	10%	
Glucocorticoid use (mg)			
Mean daily dose	22.7 (14.1)	14.8 (13.9)	0.011
Highest dose	55.3 (23.2)	37.6 (25.2)	0.001
Cytotoxic drug use†	59%	32%	0.015

Values are mean (SD) or per cent.

*Only p values ≤ 0.10 are shown.

†Cyclophosphamide, azathioprine or both.

NSAID, non-steroidal anti-inflammatory drug.

Table 4 Multivariable conditional logistic regression models for the occurrence of symptomatic osteonecrosis

Feature	OR	95% CI	p Value
<i>Model 1 (average daily dose of glucocorticoids)</i>			
Cytotoxic drug use*	3.890	1.385 to 10.928	0.010
Triglyceride level	0.990	0.980 to 0.998	0.046
Average daily dose of glucocorticoids	1.033	0.995 to 1.072	0.085
<i>Model 2 (highest dose of glucocorticoids)</i>			
Cytotoxic drug use	3.039	1.022 to 9.036	0.046
Triglyceride level	0.990	0.969 to 1.013	0.056
Highest dose of glucocorticoids	1.025	1.003 to 1.047	0.027

*Cyclophosphamide, azathioprine or both.
CI, confidence interval; OR, odds ratio.

of glucocorticoids and probably the duration of use are the most important factors underlying this known association.

Cytotoxic drugs are often given to SLE patients, particularly those with more serious disease manifestations. Our study showed that these drugs are a risk factor for the development of symptomatic osteonecrosis. It may be argued that cytotoxic drug use is only a proxy for more aggressive disease. However, no differences were observed between cases and controls in terms of disease activity, yet cytotoxic drug use remained significant in the multivariable analyses after adjusting for the use of glucocorticoids, other treatments, and other potential confounding variables. Osteonecrosis has been reported to occur in cancer patients receiving chemotherapy.^{29–31} It should be pointed out that much higher doses of cytotoxic drugs are used in oncology patients; moreover, in the majority of cases reported, glucocorticoids had been used in combination with cytotoxic drugs and thus were felt to be responsible for the association. However, an association between chemotherapy (without glucocorticoids) and osteonecrosis has also been reported.³² The association between cytotoxic drug treatment and osteonecrosis has been described previously in the Toronto lupus cohort involving 140 patients¹²; our results thus support those findings, though the mechanism underlying the association remains unknown.

We failed to identify other risk factors for the occurrence of symptomatic osteonecrosis. We tried to be inclusive in our analyses—that is, most of the factors (around 70) previously reported to be associated with osteonecrosis in lupus were considered in our preliminary analyses.⁹ However, only those factors identified in large studies, or in more than one study, were included. Such is the case for Raynaud's phenomenon, which was reported in 10 of 16 SLE patients with osteonecrosis (63%) in comparison with only 18% of those without¹⁵; this association was later corroborated in a larger cohort of SLE patients from the same institution.² Arthritis has been also reported to be associated with osteonecrosis in the Canadian study mentioned above.¹² However, we failed to confirm either association. aPL antibodies have been hypothesized to predispose to osteonecrosis because of their prothrombotic properties^{6,9}; however, this association has not been uniformly reported.^{6,9,13,14,33,34} Our data failed to support such an association, although LAC was more commonly present among the cases than the controls.

We included serum lipoprotein levels in the multivariable analyses despite not being significant in the univariable analyses, given that there were numerical differences between cases and controls and also because data from preliminary analyses including all the patients in the LUMINA cohort suggest the presence of an independent association between osteonecrosis and serum LDL cholesterol.³⁵ We could not confirm our preliminary findings,

however. Dyslipidaemia has been associated with idiopathic osteonecrosis^{36–38}; however, this association had not been reported in SLE. In fact, in a study which included 62 SLE patients who were being treated with high doses of glucocorticoids, of whom nine developed osteonecrosis, an independent negative association between serum levels of triglycerides and osteonecrosis was found, suggesting a protective effect of this lipid.²⁸ Our data support the findings from that study. Higher rather than lower levels of triglycerides have been associated with osteonecrosis in other studies.^{39,40} It is conceivable that the more aggressive management of the disease observed among patients with symptomatic osteonecrosis (higher doses of glucocorticoids and a more frequent use of cytotoxic drugs) could have resulted in a decrease in the serum levels of triglycerides as a linear relation between triglyceride levels and disease activity in SLE has been demonstrated.⁴¹

Finally, we failed to identify protective factors for the occurrence of symptomatic osteonecrosis (excluding the potential role of triglycerides). We specifically investigated the role of hydroxychloroquine, which is an immunomodulatory drug with anti-inflammatory,⁴² lipid lowering,⁴³ antithrombotic,^{44,45} and anti-platelet⁴⁶ properties, all of which may have beneficial effects in the prevention of osteonecrosis. Although our cases were less exposed to hydroxychloroquine than controls, this variable was not retained in the multivariable models examined.

Our study is not without limitations. First, sample size may have limited our ability to confirm some of the previously reported associations; however, we feel that the statistical approach that we used, a nested matched case-control study, although less powerful than one that includes all the other LUMINA patients as controls, is more appropriate, as cases and controls are adjusted for variables that affect the probability of symptomatic osteonecrosis occurring (disease duration) or that have obvious relevance such as sex, age, and ethnicity. Second, although significant efforts were made to reconstruct the details about the drug exposure data not available in the original LUMINA database (between TD and T0), this was not possible in a few of the cases and controls. Finally some of the laboratory variables, such as serum lipid levels and autoantibodies, are based on data obtained at T0 and not at TD; this may have influenced our results as some of the osteonecrosis events clearly occurred before T0.

Conclusions

In summary, we have now confirmed the association between glucocorticoid use and the development of symptomatic osteonecrosis in SLE patients; we have also identified the association between this complication and the use of cytotoxic drugs as demonstrated by Gladman *et al* several years before but never corroborated.¹² The relation between

symptomatic osteonecrosis and serum lipid levels deserves further study. There is no reason to suspect that different factors are associated with the occurrence of asymptomatic osteonecrosis, but such a study will require the systematic imaging evaluation of a large number of lupus patients which is certainly not financially feasible. The findings from our study, nevertheless, may have direct applicability to the management of lupus patients, reinforcing the view that both glucocorticoids and cytotoxic drugs should be used only when strictly indicated, in terms of both dose and duration.

ACKNOWLEDGEMENTS

We would like to acknowledge all LUMINA patients, without whom this study would have not been possible, our supporting staff (Martha L Sanchez MD, MPH, and Ellen D Sowell, AA at UAB, Carmine Pinilla MT at UPR, and Robert Sandoval BA, Li-Lu Wang MS, BS at UTH) for their efforts in securing our patients' follow up and carrying out other LUMINA related tasks, Drs Ruihua Wu and Yehuda Schonfeld for determining anti-oxidised LDL antibodies in all patients, and Ms Ella Henderson and Maria A Tyson AAs for their expert assistance in the preparation of this manuscript. Supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01-AR42503), General Clinical Research Centers (M01-RR02558 (UTH-HSC) and M01-RR00032 (UAB)), the National Center for Research Resources (NCRR/NIH) RCMI Clinical Research Infrastructure Initiative (RCRII) award 1P20RR11126 (UPR-MSC), the Mary Kirkland Scholars Award Program (UAB), and a PANLAR Fellowship Program (UAB).

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