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Predictors of the Rate of Change in Disease Activity over Time in LUMINA, a Multiethnic US Cohort of Patients with Systemic Lupus Erythematosus: LUMINA LXX

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Abstract

The objectives of the present study were (1) to clarify and quantify the relationship between age and disease duration with the rate of change in disease activity over time in patients with systemic lupus erythematosus (SLE) and (2) to explore other possible factors associated with this rate of change. To this end, SLE patients from LUMINA were studied if they had ≥ 3 visits in which disease activity (Systemic Lupus Activity Measure-Revised or SLAM-R) had been ascertained. Variables associated with the rate (slope) of change in disease activity (obtained by regressing the SLAM-R scores against the length of time from diagnosis to last visit) were examined by univariable and multivariable analyses. Five-hundred forty-two of the 632 patients had ≥ 3 SLAM-R scores. In multivariable analyses Caucasians exhibited the fastest decline in disease activity; Texan Hispanics exhibited the slowest, trailed by the African Americans. Longer disease duration and *HLA-DRB1*1503* positivity were associated with a slower decline whereas a greater number of ACR criteria and abnormal laboratory parameters (white blood cell and platelet counts, hematocrit and serum creatinine) were associated with a faster decline. These findings complement existing knowledge on SLE disease activity and are potentially useful to clinicians managing these patients.

Keywords

Lupus; disease activity; rate of change; ethnicity; cohort

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by flares and remissions. Active disease is associated with a reduced quality of life, damage accrual, and early mortality (1–3). A number of studies have been conducted to better understand the

changes in disease activity over time and the occurrence and predictors of flares and remissions. Barr et al, for example, identified three patterns of SLE disease activity (relapsing-remitting, chronic active, and long quiescent) based on plots of physician's global assessment and modified SLE Disease Activity Index (SLEDAI) scores against time (4). A number of researchers, including us, have examined factors associated with persistently high levels of disease activity as well as with reductions in disease activity levels (5–10). In general, disease activity in SLE patients declines with longer disease duration and older age (11, 12).

The objectives of the current study were to 1). clarify and quantify the relationships between age and disease duration with the rate of change in disease activity over time, and 2). explore other factors associated with the rate of change in disease activity over time in LUMINA (Lupus in Minorities: Nature vs. Nurture), a multiethnic cohort of SLE patients.

Patients and Methods

Study Subjects

The patients participating in the study were from the LUMINA cohort. As previously described, LUMINA is an on-going longitudinal cohort of lupus patients established in 1994 (5, 13). At enrollment, all patients met the revised and updated American College of Rheumatology (ACR) criteria for the classification of SLE (14, 15), had a disease duration of 5 years or less, were 16 years of age or older, of defined ethnicity [Hispanic (Texan or Puerto Rican), African American, and Caucasian], and were living in the geographical recruitment areas of the participating centers (The University of Alabama at Birmingham, The University of Texas Health Science Center at Houston and The University of Puerto Rico Medical Sciences Campus). The study was approved by the Institutional Review Boards of the participating institutions and was conducted in accordance with the Declaration of Helsinki's guidance for research in humans.

Detailed description of patient recruitment and follow-up had been published previously (5, 13). Briefly, eligibility was confirmed by the principal investigator at each participating center. Prior to enrollment, all medical records were abstracted to obtain demographic and clinical information from the time of diagnosis (TD) to the time of enrollment (T0). Subjects were considered incident cases if the time between TD and T0 was six months or less; 25% of patients in the cohort met this definition, hence incident cases. Follow-up visits were conducted every six months during the first year and yearly thereafter. At baseline and each visit the patients completed several questionnaires and underwent a physical examination and laboratory tests; medical records were also reviewed. Data for missed visits were obtained from all available medical records.

Variables

The LUMINA cohort database contains information on socioeconomic-demographic, clinical, immunologic, genetic, psychological and behavioral characteristics of the patients (5, 13). Only the variables that were included in the present study will be described.

Socioeconomic-demographic and life-style characteristics were self-reported at T0, which included age, gender, ethnicity, marital status, income, number of years of education, smoking, exercising, and having health insurance. Income is categorized as being above or below the Federal Government-defined poverty threshold line after adjusting for the number of individuals living in the household (16). Health insurance status at TD was used; if unavailable, status at T0 was used instead.

Disease activity was ascertained with the Systemic Lupus Activity Measure – Revised (SLAM-R) (17) and the data were obtained during study visits. Disease activity at TD for non-incident cases and missed visits were assessed based on available records from review of medical records, a validated method described by Wluka et al (18). The laboratory parameters examined included those from the SLAM-R at TD and they were hematocrit, white blood cell (WBC), lymphocyte and platelet counts, erythrocyte sedimentation rate (ESR), creatinine and urinalysis. Serum C-reactive protein was measured at T0 by a high sensitivity immunometric assay (Immunelite 2000 Diagnostic Products, Los Angeles, CA, US). Anti-double-stranded DNA (dsDNA) antibodies were measured using a *Crithidia luciliae* assay (20). Antinuclear antibodies (ANA) were examined by indirect immunofluorescence with Hep-2 cells as substrate. Anti-Smith, anti-Ro, and anti-La antibodies were assessed by immunodiffusion. Antiphospholipid (aPL) IgG and IgM antibodies were determined by enzyme-linked immunoabsorbent assays whereas the lupus anticoagulant (LAC) was examined by the staclot test (Diagnostica Stago 92600, Asnières-Sur-Seine, France) (21, 22).

The use of hydroxychloroquine, glucocorticoids and immunosuppressive medications (route of administration, dose and duration, if applicable) was obtained from both interviews and medical records review. Disease damage was ascertained using the Systemic Lupus International Collaborating Clinics (SLICC) / ACR Damage Index (SDI) (19). Disease duration was defined as the time between TD and the most recent visit (TL). Disease onset was considered to be acute if the ACR SLE classification criteria were accrued within four weeks and insidious, if otherwise. Menopausal status was categorized as post-menopausal if menopause had occurred during the study period, regardless of the cause, and pre-menopausal if otherwise.

Selected *HLA-DRBI*, *HLA-DQBI*, and *HLA-DQAI* specificities were included in these analyses. To this end genomic DNA was extracted using the PureGene kit (Gentra Systems, Minneapolis, MN) following the manufacturers recommendations; genotyping was performed as previously described (23).

Behavioral and psychological variables included were helplessness (ascertained with the Rheumatology Attitude Index) (24), social support [assessed with the International Support Evaluation List (ISEL)] (25), and abnormal illness-related behaviors [assessed with the Illness Behavior Questionnaire (IBQ)] (26); these variables were all from T0.

Self-perceived health-related quality of life was assessed using the Medical Outcome Study Short Form-36 (SF-36), a 36-item validated instrument, which evaluates physical and mental functioning as two separate summary measures (27).

Statistical analyses

Only patients in whom three or more measures of disease activity have been obtained at different time points since SLE diagnosis (TD) were included in these analyses. The dependent variable for this study is the rate or slope of change in disease activity over time; this slope was derived for each patient by regressing the SLAM-R scores (dependent variable) against the length of time (independent variable) from TD (T0 if incident cases) to the time when the score was recorded. The slope reflects the change in disease activity over time; a negative value indicates a decline in disease activity whereas a positive value indicates an increase. The absolute value is indicative of the rate of change; a high absolute value reflects rapidly increasing or decreasing disease activity whereas a low value reflects the opposite.

Univariable linear regression analyses were performed to identify potential predictors of the slope; variables with p -value ≤ 0.05 in these analyses were then included in an initial multivariable linear regression model. Backward elimination was performed to produce a final parsimonious model. In alternative analyses limited to women the impact of menopausal status was assessed. A p -value ≤ 0.05 was indicative of statistical significance in all multivariable analyses.

Parameter estimates in the linear regression analyses provide information on how the baseline characteristics predict the general pattern of disease activity. A positive parameter estimate indicates that the presence of the characteristic is associated with slower rate of decline and a negative value with a faster rate of decline. When the potential predictor is a continuous variable, a positive parameter estimate indicates that the higher the value the slower the rate of decline in disease activity (e.g., older age at T0).

To test the validity of the results, sensitivity analyses were performed in three patient subgroups: 1). subjects who had five or more measures of disease activity during the study period ($n=469$); 2). incident cases ($n=153$); 3) non-incident cases ($n=389$).

Results

Of 632 patients in the LUMINA cohort, 542 had three or more SLAM-R scores recorded and were included in these analyses. Among them, 90.3% were women ($n=475$), 91 were Texan Hispanics, 101 Puerto Rican Hispanics, 190 African Americans, and 160 Caucasians. The mean age at baseline and average total disease duration from diagnosis to the last follow-up visit were 35.8 and 6.0 years, respectively. The average slope was -0.87 (standard deviation, 2.19), indicating that on average, patients experience a 0.87 point decline in disease activity per year. Figure 1 plots the average SLAM-R score on the Y-axis and total disease duration from TD to the last visit on the X-axis. Data beyond 14 years are not plotted because of the relatively few patients ($n<20$) reaching this time point.

The mean and standard deviation (SD) for age at baseline and total disease duration for the following subgroups of subjects were: 1) subjects with five or more measures of disease activity: 37.4 (SD: 12.5) and 7.1 (SD: 3.3) years; 2) incident cases: 35.9 (SD: 11.8) and 4.8 (SD: 2.9) years; 3) non-incident cases: 37.3 (SD: 12.7) and 7.2 (SD: 3.5) years.

Univariable analyses

Older age and female gender were associated with a slower rate of decline in disease activity. No significant association was observed between other socioeconomic-demographic characteristics with the outcome. A greater number of ACR criteria at TD and acute onset were associated with a faster rate of decline in disease activity. On average, patients experienced a gradual decline in disease activity but the rate of decline slowed down as disease duration increased. Among the laboratory parameters examined, low hematocrit, low WBC, lymphocyte and platelet counts, elevated creatinine and abnormal urinary sediment were associated with a faster rate of decline in disease activity. Other laboratory parameters, including ANA and antibodies to dsDNA, Ro, La, Sm, RNP, IgG and IgM aPL, LAC, CRP and ESR were not significantly associated with the outcome. The presence of *HLA-DRB1*1503* was associated with a slower rate of decline and no association was observed for either *HLA-DQA1*0501*, *DQB1*0201*, *DQB1*0602*, *DRB1*08*, and *DRB1*0301*. The use of non-selective NSAIDs was associated with a slower rate of decline in disease activity whereas higher weighted doses of glucocorticoids were associated with a faster rate of decline. These data are depicted in Table 1. All other medications, including the immunosuppressants cyclophosphamide and azathioprine, and hydroxychloroquine were not associated with either a faster or a slower rate of decline of

disease activity (data not shown). Likewise, none of the psychosocial and behavioral variables and other clinical and laboratory parameters was significantly associated with the slope (data not shown).

Multivariable analyses

The fastest decline in disease activity was observed among the Caucasian patients (reference group) while the Texan Hispanics had the slowest rate of decline in comparison, trailed second by African Americans. The number of ACR criteria at TD, and disease duration remained significant predictors of the slope. The same was the case for the following laboratory tests: WBC count, hematocrit, serum creatinine and *HLA-DRB1*1503*. The associations with weighted glucocorticoid doses and NSAIDs were no longer evident. These data are also depicted in Table 1. When the analyses were limited to women to examine the impact of menopausal status on the slope, no association was found (data not shown).

The results of the sensitivity analyses for patients with five or more visits and for incident and prevalent patients separately, are presented in Table 2. The parameter estimates measure the direction and magnitude of the association between patient characteristics with the slope. While some of the parameter estimates differed in magnitude from those of the original model, the direction of the association remained the same for all four models, providing support to the validity of the analyses presented in Table 1.

Discussion

This is the first study that explores the factors associated with the slope in disease activity, which conveys a general pattern of its change over time. In a study carried out in the Toronto Lupus cohort the slope *per se* was not found to add information in the prediction of damage and mortality when added to models that already included the adjusted mean disease activity (28). The pattern of disease activity in and of itself, however, may represent an outcome of interest given that active disease is a significant component of SLE-related morbidity and an independent predictor of damage accrual.

Our analyses demonstrate that disease activity decreases at a steady rate after a steep decline immediately after disease diagnosis as depicted in Figure 1. After controlling for other variables age was no longer a significant predictor. Gender differences were observed in the univariable analyses with women experiencing a slower decline in disease activity than men; however, gender was not retained in the multivariable analysis. A state of hypoestrogenemia has been suggested to be associated with reduced disease flares (29, 30); however, we did not find menopausal status to be a significant predictor of the slope in our analyses, a finding that is consistent with previous reports in which disease duration rather than menopause contributed to the amelioration of disease activity (11, 31). We have previously shown that African Americans and Texan Hispanics tend to have higher levels of disease activity over time (6). Consistent with this notion, we found that Texan Hispanic patients had the slowest rate of decline in disease activity, trailed by the African American patients. This may explain why these patients tend to accrue more damage over the course of the disease than patients from other ethnic groups (32).

An array of laboratory tests has been found to be a strong predictor of disease flares by a number of different investigators (10, 33). In this study, abnormal laboratory results early in the course of the disease and the number of ACR criteria were predictive of a faster decline in disease activity, suggesting perhaps that patients presenting with more severe disease at diagnosis are more likely to experience a rapid reduction in disease activity to the level of those who started with less active disease. Anti-dsDNA antibodies which have been shown to be associated with higher levels of disease activity in our cohort (6) and predictors of

subsequent disease flares by others (10, 34) were not found to be associated with the slope in our analyses. Of note, in a longitudinal study conducted by van den Berg et al anti-dsDNA antibodies were not predictive of long-term disease activity even though they were significant predictors of subsequent disease flares; this may explain the lack of association found in our study (35). The independent association of *HLA-DRB1*1503* and a slower rate of disease activity decline over time is of interest, although an explanation for such association is not self-evident; given that this HLA specificity is preferentially expressed in African Americans this association may merely be a proxy for this ethnic group.

Although some of the medications were associated with either a faster or a slower rate of decline in the univariable analyses (NSAIDs and the weighted dose of glucocorticoids) they were not retained in the multivariable analyses. Furthermore, neither immunosuppressants nor hydroxychloroquine were associated with the rate of decline in disease activity. One possible explanation for the lack of an observed association is confounding by indication (36). In our study, while we adjusted for disease severity at diagnosis, medication use was examined for the entire study period consequently resulting in incomplete adjustment of confounding by indication. Another possible explanation (and limitation) for the lack of impact of medications on the slope is the fact that patients were categorized as ever vs. never users, an approach that does not allow the differentiation of doses, frequency and duration of use as well as compliance, therefore, possibly biasing the results towards the null.

The main limitation of our study is the relative infrequency of study visits which were conducted yearly after the first year from enrollment. As a result, disease activity between study visits was not captured and it is possible that the time points at which disease activity were measured may not be representative of the average disease activity the subjects experienced at the time period. Ideally, more frequent assessments of disease activity than the ones done by us in this study may better define the changes in disease activity over time and to derive a more precise slope; our study, nevertheless, has a number of advantages; it uses a longitudinal analytical approach to examine data obtained for 12 years in an ethnically diverse cohort. Moreover, the database contains comprehensive information that allows us to assess a large number of disease and patient-related characteristics.

In conclusion, we found a number clinical and laboratory variables to be significant predictors of the rate of change in disease activity over time in a multiethnic US cohort of patients with SLE. These findings complement existing knowledge on SLE disease activity and are potentially useful to clinicians managing these patients.

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Figure 1.
SLAM-R scores over the duration of the disease in LUMINA patients

Table 1

Variables Associated with the Pattern of Change of Disease Activity over Time (slope) in LUMINA* Patients by Univariable[†] and Multivariable Analyses[‡]

Variable	Univariable		Multivariable	
	Parameter estimate	p value	Parameter estimate	p value
Demographic features				
Age, years	0.017	0.027		
Gender (female)	0.721	0.023		
Ethnicity [‡]				
Texan Hispanic	0.297	0.304	0.594	0.027
Puerto Rican Hispanic	0.111	0.691	0.192	0.454
African American	0.071	0.762	0.354	0.151
Disease features				
ACR [§] criteria number at diagnosis	-0.585	<.0001	-0.462	0.001
Acute onset	-0.793	0.004		
Disease duration (years)	0.140	<.0001	0.131	<.0001
Laboratory features				
Hematocrit (lower)	-0.806	<.0001	-0.636	0.001
White blood cell count (lower)	-0.678	0.005	-0.592	0.011
Lymphocyte count (lower)	-0.520	0.006		
Platelet count (lower)	-1.109	0.0003		
Serum creatinine (higher)	-1.421	<.0001	-1.195	0.0001
Urine sediment (abnormal)	-0.805	<.0001		
Genetic features				
<i>HLA-DRB1*1503</i>	0.632	0.018	0.793	0.004
Medications				
Weighted glucocorticoids	-0.027	0.015		
NSAIDs [¶]	0.497	0.010		

* Lupus in Minorities: Nature vs Nurture;

[†] all variables described in the text were examined; only the significant ones and those entered in the multivariable analyses are listed in this Table;

[‡] Caucasian is the reference group;

[§] American College of Rheumatology;

[¶] Non-steroidal antiinflammatory drugs.

Table 2

Variables Associated with the Pattern of Change of Disease Activity over Time (slope) in sub-groups of LUMINA* Patients

	Subjects with five or more measures of disease activity n=469 [#]	Incident Cases n=153 [#]	Non-incident Cases n=389 [#]
Demographic features			
Ethnicity [‡]			
Texan Hispanic	0.420*	0.609	0.721*
Puerto Rican Hispanic	0.141	0.273	0.178
African American	0.209	1.050	0.125
Disease features			
ACR [§] criteria number at diagnosis	-0.342*	-0.619*	-0.355*
Disease duration (years)	0.080*	0.284*	0.074*
Laboratory features			
Hematocrit (lower)	-0.303*	-1.255*	-0.417*
White blood cell count (lower)	-0.284*	-1.723*	-0.192
Serum creatinine (higher)	-1.086*	-1.251*	-1.004*
Genetic features			
HLA-DRB1*1503	0.416*	1.275*	0.695*

* Lupus in Minorities: Nature vs Nurture;

* Statistical significance achieved;

[‡] Caucasian is the reference group;

[§] American College of Rheumatology.

[‡] The reference group is Caucasian ethnicity.

[#] The numbers of subjects with complete data for the multivariable models were 468, 152, and 383, respectively, for each group.