Persistent Disease Activity Remains a Burden for Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Persistent systemic lupus erythematosus (SLE) disease activity is associated with increased morbidity and mortality. In a multicenter cohort of patients with prevalent SLE, we described persistence, patterns, and predictors of change in disease activity over time.

Methods. Based on SLE Disease Activity Index (SLEDAI)-2K scores at cohort entry, patients were classified into 4 groups: low (score < 4; LOW), moderate (4 to < 6; MOD), moderately high (6 to ≤ 10; MHIGH), and very high (> 10; VHIGH). Multivariable linear and longitudinal mixed linear regression models were used to identify predictors of change over time in SLEDAI-2K.

Results. There were 2019 participants, with declining followup data over 5 years (1326, 580, 274, 186, and 148 patients, respectively). At cohort entry, mean (± SD) age was 42 (± 17) years, disease duration 11 (± 10) years, and 90% were female. The 4 groups included 44% LOW (n = 891), 20% MOD (n = 400), 22% MHIGH (n = 442), and 14% VHIGH (n = 286); therefore, 36% had clinically important SLE activity. The proportion of patients in the LOW group at entry who moved to a higher activity level varied from 30% (167/557) at 1 year, to 49% (41/83) at 3 years, and 54% (30/56) at 5 years. Among 181 patients with MOD to VHIGH entry activity and 3 years of followup, 116 (64.1%) remained active. In all analyses, only higher SLEDAI-2K at cohort entry remained a significant predictor of higher SLEDAI-2K in subsequent years.

Conclusion. Higher SLEDAI-2K at study entry was the single major independent predictor of higher SLEDAI-2K over time, reflecting frequent persistence of active disease, even in patients with longstanding disease. This highlights gaps in the optimal treatment of SLE. (First Release September 15 2018; J Rheumatol 2019;46:166–75; doi:10.3899/jrheum.171454)

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease that manifests itself in many different organs in the body, primarily affecting women. SLE is a difficult disease to treat because of its heterogeneous features: no two patients are the same. Treatment aims to control disease activity and prevent damage. Damage reflects the accumulated and irreversible loss of organ function owing to either the disease itself or its treatment. Treating physicians must therefore offer patients the best treatment options that will balance the tradeoffs between risk of treatment side effects from intensive immunosuppressive therapy versus poor control of the disease, with the potential for irreversible critical organ damage.

While modern treatments for SLE have led to decreased mortality rates overall, mortality still remains unacceptably high compared to the general population[1], and many patients have ongoing active disease in spite of treatment[2]. Persistent high disease activity over time has been clearly linked to both morbidity and mortality and is associated with accelerated damage accrual[3,4]. Similarly, treatments used commonly in SLE, in particular corticosteroids, also contribute to an accrual of both global and specific organ damage over time[1,5,6]. It is recognized that control of disease activity for many patients is suboptimal; only a small percentage achieve longterm remission that is sustained with no or minimal treatment[7]. While multiple treatments have been investigated in recent years, many have failed[8–14] and many treatment options to reduce disease activity and limit corticosteroid use are not fully effective.

The aim of our study is to describe the distribution of levels of disease activity, both at cohort entry, in cross-sectional analyses, and longitudinally, in a cohort of prevalent patients with SLE, and to assess its associations with clinical characteristics. In addition, we examined changes in disease activity over time, and predictors of these changes. Suboptimal disease control, or persistently active SLE, has been identified as an ongoing burden for patients with SLE[1,15]. Information from this cohort will provide a clearer understanding of the burden of persistently active SLE.

MATERIALS AND METHODS

The 1000 Canadian Faces of Lupus study is a prospective multicenter study of SLE in Canada, enrolling patients from 2005 to 2008. Patients were enrolled at 14 sites across Canada, 10 adult and 4 pediatric rheumatology clinics. A detailed description of enrollment criteria and variables collected has been previously published[16]. Patients were eligible if they were identified by the site investigator(s) as having a clinical diagnosis of SLE. Both incident and prevalent cases were included. Because funding terminated shortly after the enrollment period ended, the number of annual followup visits available for analysis gradually declined.

Study variables. At the initial visit, all available medical records were reviewed by the site investigators, and clinical data were abstracted and entered onto a comprehensive standard form. Clinical manifestations of SLE were recorded, including those forming the American College of Rheumatology (ACR) criteria[17] and those included in the revised Systemic Lupus Activity Measure (SLAM-R) and the revised SLE Disease Activity Index (SLEDAI-2K)[18,19]. In addition, autoantibody status was recorded for anti-dsDNA, anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB, and antiphospholipid antibodies (aPL; includes anticardiolipin antibodies and lupus anticoagulant). "Ever positive" results were collected from the medical record at the initial visit, while blood was tested at entry and annually to determine current status for antinuclear antibodies (ANA; anti-dsDNA, anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB, and aPL). Disease activity was measured at entry and annually using the SLEDAI-2K validated SLE activity scale[18,19]. Patients also filled out the Systemic Lupus Activity Questionnaire (SLAQ)[20], a validated self-reported measure of disease activity, at entry and each followup visit, which includes a visual analog scale for global disease activity and fatigue. Current and past medication use were recorded and updated at each visit, and patients filled out a generic health status measure, the Medical Outcomes Study Short Form-36[21]. Components of the Systemic Lupus International Collaborating Clinics/ACR Damage Index[22,23] were abstracted from the medical records and reviewed with the patients during the interview, and updated annually. Detailed sociodemographic data were collected including age, sex, highest education achieved, total household income, and self-reported ethnicity based on the format and categories used by Statistics Canada[24]. For the purposes of our analysis, patients were categorized according to the main self-chosen ethnic category.

Statistical analyses. Initially, data at cohort entry (Year 0) were analyzed, and 4 groups were created based on their SLEDAI-2K score: low (< 4), moderate (4 to < 6), moderately high (6 to < 10), and very high (> 10). These groupings were chosen by the investigators based on a SLEDAI score ≥ 6 as the standard definition of active SLE requiring treatment changes, with some investigators suggesting a score of 3 or 4 should define active disease[25,26]. We performed cross-sectional comparisons of the entry characteristics of the 4 groups, corresponding to different disease activity levels, using bivariate analyses: chi-square tests for categorical variables, as well as 1-way ANOVA and tests for trend for continuous variables. Patients who had sufficient followup duration were then classified into 4 similar disease activity groups at 1, 2, 3, 4, and 5 years after the initial visit. The results of the 6 groupings (years 0–5) were then cross-tabulated to estimate the probabilities of longitudinal transitions between activity levels at different times.

To determine cohort entry predictors of changes in disease activity during the first year after cohort entry, we relied on multivariable linear regression. SLEDAI-2K score (log-transformed because of the highly skewed distribution) at 1 year after cohort entry was used as the outcome variable. Potential predictors included cohort entry values of sociodemographic variables, ACR criteria, extractable nuclear antigens, aPL, current use of treatment, and the cohort entry (Year 0) SLEDAI-2K score. The final model was selected based on stepwise backward selection, with the $p > 0.15$ criterion for variables elimination, corresponding roughly to the Akaike information criterion[27]. Multiple Imputations by Chained Equation (MICE) was used to deal with missing data[28] (section A1 of Supplementary Data 1, available with the online version of this article).

In separate, longitudinal analyses, we assessed predictors of SLE activity during the followup. In these analyses, SLEDAI-2K scores at years 1–5 were used as repeated measures of the outcome. Entry predictors included sociodemographic variables, ACR criteria, serology and current treatment, as well as the cohort entry SLEDAI-2K score. To account for both the between-subjects variation in the values of SLEDAI-2K scores and within-subject correlation of the repeated-over-time scores, we used linear mixed models in all longitudinal analyses, with a random intercept, and the first order autoregressive correlation structure[29]. Section A2 of Supplementary Data 1 (available with the online version of this article) describes handling of missing data in longitudinal analyses.

Two different repeated-measures linear mixed models were estimated, each addressing a different research question. The 2 models differed in the way that years of followup, corresponding to consecutive measurements of the SLEDAI-2K score, were analyzed. The first model included only the main effect of followup time as an adjustment covariate, and thus assessed

the ability of cohort entry characteristics to predict the average-over-time level of disease activity during the followup. Similar to the linear regression analyses, the final model was selected through backward elimination, with $p > 0.15$ criterion for elimination. The second mixed linear model helped assess whether and how the associations between individual entry characteristics and post-entry repeated measures of SLEDAI-2K score varied with increasing followup time. To this end, the model included a series of 2-way interactions between (1) each of the entry variables, and (2) a time-varying covariate representing the followup time, in years since cohort entry. Then, we used backward elimination, with a $p > 0.05$ cutoff, to select statistically significant interactions with followup time, while forcing the main effects of all entry predictors and the followup time. A significant interaction with a given entry predictor would indicate whether its association with post-entry SLEDAI-2K score becomes either weaker or stronger, with increasing time since cohort entry, depending on the sign of the interaction coefficient[30].

The 1000 Faces of Lupus study was approved by the regional Research Ethics Boards at each participating site, and this secondary analysis was approved by the University of Manitoba Health Research Ethics Board [HS14458(H2005:104)]. All patients provided informed written and verbal consent. Statistical analyses were conducted using RStudio 0.99.903[31].

RESULTS

The cohort included 2019 patients. Mean age at cohort entry was 42 (SD 17) years; 90% were female, 63% were white, with a mean age at diagnosis of 31 (SD 15) years. Followup data were available for 1326, 580, 274, 186, and 148 patients at 1, 2, 3, 4, and 5 years, respectively. During the 5 years of observation, the median times between consecutive prescheduled yearly visits did not vary systematically either across the 4 disease activity groups or the followup time, and always ranged from about 11 to about 13 months (336–399 days). Demographic data for the 4 disease activity groups are presented in Table 1. Mean disease duration at cohort entry was 11.1 (SD 10.1) years, but was slightly less in those with very high disease activity, at 9.1 years, compared to 11.7 in those with low disease activity ($p < 0.001$). Patients with very high disease activity were also more likely to have lower incomes (Table 1), with 37.3% having incomes < $30,000 compared to 25.0% in the low disease activity group ($p = 0.006$). As expected, those in the higher disease activity groups also had higher physician's global assessment (PGA) disease activity scores, SLAM-R, and SLAQ scores, had met a higher number of ACR classification criteria, and were more likely to have had renal involvement (Table 2).

There were no differences in antimalarial use across disease activity groups, with close to 70% of patients taking these medications at their baseline visit. As expected, prednisone use at cohort entry was highest in the very highly active group at 64%, but was markedly high at about 40% even in those with low disease activity ($p < 0.001$; Table 3). Azathioprine and mycophenolate use did not differ between groups, while cyclophosphamide use, though infrequent, was most common in those with very highly active disease ($p < 0.001$). As expected, the overall proportion of patients taking immunosuppressants was highest in those with very highly active disease.

Prednisone dose was available for only a subset of patients (Table 3). Mean daily prednisone dose was 24 mg in the very highly active group, and about half that dose (11–13 mg) in each of the other groups ($p = 0.001$). Daily doses > 7.5 mg were prescribed to one-third of very highly active patients and about 15% of those with low or moderate disease activity ($p < 0.001$).

Table 4 shows probabilities of a patient transitioning from 1 disease activity group to another, based on the SLEDAI-2K scores over 2 consecutive yearly visits. For example, patients with low disease activity at cohort entry had a 71% probability of having low activity 1 year later, and only a 5% probability of becoming very highly active. In contrast, a patient with very high initial disease activity had a probability of < 20% of attaining low disease activity 1 year later, and a 36% probability of continued very high disease activity. Across the years, patients with moderately high disease activity had about 50% probability of continued moderately high or very high disease activity 1 year later, whereas patients with low disease activity had about 14–25% probability of progressing to at least moderately high disease activity (Table 4). Figure 1 shows patients categorized by level of disease activity at cohort entry and describes their transitioning to specific disease activity groups across the followup time. For example, close to half of the initial low activity patients remained in this category throughout the followup (Figure 1a), whereas patients whose SLE was initially very highly active had about equal (15–35%) probabilities of moving into each of the 4 categories during the subsequent years of followup (Figure 1d).

In multivariable linear regression analyses, we used quantitative SLEDAI-2K scores rather than the 4 groups of disease activity to increase precision. Among SLE patients with the same entry SLEDAI-2K score, those with longer disease duration at cohort entry ($p = 0.020$) and highest income category ($p = 0.015$), patients without arthritis ($p = 0.049$) and women ($p = 0.057$) had lower SLE activity at 1 year after study entry (Table 5). However, as expected, the initial SLEDAI-2K score had by far the strongest association with the 1-year score (t statistic = 16.3, $p < 0.0001$, vs t statistics < 2.9 for all other entry predictors). For each additional 1-point increase of the initial SLEDAI-2K score, the SLEDAI-2K score at 1 year increased by 0.37 points (95% CI 0.32–0.42).

In the first multivariable repeated measures linear mixed model, among all entry characteristics, only higher initial SLEDAI-2K score (t statistic = 15.15, $p < 0.0001$) and lower initial income (t statistic = 1.67, $p = 0.095$) were at least marginally statistically significant predictors of average over-time SLEDAI-2K during the followup. A 1-unit increase of the entry SLEDAI-2K score was associated, on average, with a 0.32-unit increase of the SLEDAI-2K score during the followup (95% CI 0.28–0.36; data not shown).

In the second multivariable mixed linear model, the only significant interaction with followup time involved the initial

Table 1. Demographics of patients with SLE at cohort entry, by disease activity group.

Variables	N	Disease Activity Group, Entry SLEDAI-2K Score				p for Between-group Differences		
		Low, < 4 n = 891 (44%), 95% CI 42–46	Moderate, 4 to < 6 n = 400 (20%), 95% CI 18–22	Moderately High, 6 to ≤ 10 n = 442 (22%), 95% CI 20–24	Very High, > 10 n = 286 (14%), 95% CI 13–16	ANOVA	Chi-square Test	Test for Trend
Female, %	2009	88.7	88.9	92.5	89.4		0.167	0.230
Age, yrs, mean (SD)	1884	42.2 (18.3)	41.8 (16.2)	43.1 (16.1)	39.0 (14.6)	0.018		0.110
Disease duration, yrs, mean (SD)	1932	11.7 (10.4)	11.8 (9.8)	10.4 (10.0)	9.1 (9.4)	< 0.001		< 0.001
Age at diagnosis, yrs, mean (SD)	1844	30.4 (15.9)	29.6 (14.5)	32.5 (15.5)	29.7 (13.7)	0.036		0.492
Ethnicity, %	1888						0.109	0.57
White		62.6	64.4	67.6	56.4		(white vs all other)	
All non-white		37.4	35.6	32.4	43.6			
Indigenous		3.6	4.2	5.1	4.6			
Asian		17.7	16.2	13.3	17.6			
Black		9.3	7.6	6.3	13.0			
Other		6.8	7.6	7.7	8.4			
Completed high school, %	1742	86.6	82.7	84.3	83.5		0.564	0.465
Total household income, %*	944						0.078	0.006
< $15,000		12.0	8.2	12.3	19.4			
$15,000–$29,999		13.0	15.4	15.1	17.9			
$30,000–$49,999		22.7	29.1	24.6	23.1			
≥ $50,000		52.3	47.3	48.0	39.6			

* Canadian dollars. SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.

SLEDAI-2K score ($p < 0.001$). The estimated interaction coefficient indicated that the strength of the association between the entry and post-entry values of SLEDAI-2K score gradually decreased with increasing followup time. For example, after 4 years of followup, the effect of the entry SLEDAI-2K decreases to about one-half of its effect on the SLEDAI-2K score at 1 year. However, even after 4 years of followup, higher entry score predicts a significantly higher updated score (data not shown).

DISCUSSION

Disease activity in SLE is generally thought to be highest early in the course of the disease, declining somewhat over time[32]. This premise is consistent with the overall mean SLEDAI-2K score of 4.7 that we found in this cohort of prevalent patients with longstanding disease. Other authors have reported similar scores: in a Czech study, mean SLEDAI was 3.7 after nearly 8 years[33], while in the Hopkins Lupus cohort, mean SLEDAI was 3.5 after 5 years of disease[5]. However, in spite of low mean disease activity, 36% of the participants had active SLE at cohort entry, with > 20% of those with followup data remaining active over the followup period, and at least one-third of patients had active disease at any given followup visit, as indicated by SLEDAI-2K ≥ 6. Moreover, > 40% of our patients with inactive disease (SLEDAI-2K < 6) were taking prednisone, and more than one-third required immunosuppression, reflecting rates generally similar to patients with active or very active disease. Among 600 patients from sites where prednisone dose was recorded, ~15% of the patients in the low to moderately high disease groups were taking > 7.5 mg/day, and one-third of highly active patients were taking > 7.5 mg of prednisone per day. Prednisone doses > 7.5 mg/day are known to predict increased damage accrual over time[34]. A large Spanish cohort study has reported similar findings: 15% of 3568 patients had active disease (as defined by the SLEDAI ≥ 6), after a mean of about 8 years of disease, and more than half of all patients were taking prednisone[2]. This high frequency of prednisone and immunosuppressive treatment in these patients suggests that significant ongoing treatment is required to maintain even a relatively low level of disease activity.

We also found that the probability of a patient with quiescent disease becoming active, or flaring, at some time during the followup, was substantial. Those in the lowest disease activity group, SLEDAI-2K < 4, had a 30–50% likelihood of transitioning to more active disease in the next year (Table 4). Only a minority of patients achieved lasting low disease activity states, even with treatment (Figures 1a and 1b). Conversely, those with active disease (SLEDAI-2K > 6, and SLEDAI-2K > 10) had about 30% probability of remaining active over the followup period (Figures 1c and 1d). Other authors have reported similar findings. In 1999, Barr, *et al* also reported that the long-quiescent pattern (clinical SLEDAI = 0 for at least 1 year) was uncommon, seen in only 16% of patients, while about half were persistently active for at least 1 year[35]. Zen, *et al* found that only about 21% of patients achieved prolonged (≥ 5 yrs) remission

Table 2. Disease activity, clinical manifestations, and damage.

Variables	N	Disease Activity				P values for Between-group Differences		
		Low	Moderate	Moderately High	Very High	ANOVA	Chi-square Test	Test for Trend
SLEDAI-2K, mean (SD)	2019	1.1 (1.1)	4.1 (0.3)	7.0 (1.0)	13.5 (4.6)			
SLAM-R, mean (SD)	1943	5.5 (4.8)	7.1 (3.9)	8.4 (4.7)	10.5 (6.4)	< 0.001		< 0.001
PGA VAS, mean (SD)	1943	7.7 (14.7)	11.4 (21.0)	14.8 (24.1)	23.5 (32.6)	< 0.001		< 0.001
SLAQ, mean (SD)	630	10.5 (10.1)	13.8 (10.2)	15.7 (10.8))	22.9 (13.5)	< 0.001		< 0.001
SF-36, mean (SD)								
PCS	910	40.4 (12.0)	40.5 (12.1)	39.4 (14.1)	36.8 (11.4)	0.453		0.205
MCS	910	46.9 (12.3)	46.3 (11.6)	44.7 (11.9)	43.8 (12.4)	0.395		0.127
ACR classification criteria met at cohort entry								
No. met, mean (SD)	1736	5.53 (1.61)	5.55 (1.56)	5.69 (1.74)	5.94 (1.64)	0.005		< 0.001
Individual criteria, % (N)								
Malar rash	1902	55.7 (849)	60.4 (373)	59.2 (412)	59.6 (267)		0.356	0.168
Discoid rash	1812	15.1 (830)	12.4 (347)	15.2 (387)	11.3 (248)		0.320	0.286
Photosensitivity	1867	47.3 (842)	50.0 (363)	50.7 (402)	50.2 (260)		0.843	0.506
Oral/nasal ulcerations	1869	50.0 (846)	44.1 (363)	53.8 (398)	55.0 (262)		0.003	0.001
Arthritis	1944	73.0 (866)	77.0 (383)	85.1 (422)	84.6 (273)		< 0.001	< 0.001
Serositis	1844	31.9 (836)	30.6 (359)	34.5 (397)	36.5 (252)		0.372	0.142
Renal	1867	36.4 (838)	42.3 (369)	40.4 (403)	49.8 (257)		0.001	< 0.001
Neurologic	1923	9.3 (817)	6.9 (346)	8.0 (386)	14.4 (250)		0.013	0.131
Hematologic	1923	72.9 (859)	76.5 (383)	67.5 (418)	73.4 (263)		0.036	0.362
Immunologic	1923	81.0 (863)	85.8 (386)	82.6 (419)	88.6 (271)		0.015	0.013
ANA	1939	96.8 (874)	96.4 (392)	97.0 (426)	94.8 (270)		0.433	0.278
Serology, ever positive*, % (N)								
dsDNA	949	76.6 (402)	81.2 (181)	87.1 (217)	86.6 (149)		0.004	< 0.001
Anti-Ro/SSA	1605	32.4 (707)	39.3 (313)	35.0 (351)	39.3 (234)		0.091	0.071
Anti-La/SSB	1593	13.9 (707)	14.3 (308)	15.0 (347)	17.7 (231)		0.539	0.184
Anti-Sm	902	24.6 (391)	30.2 (169)	22.2 (203)	33.8 (139)		0.052	0.199
Anti-RNP	1598	24.1 (706)	26.9 (309)	29.1 (347)	37.3 (236)		0.001	< 0.001
aPL	899	49.5 (392)	46.1 (165)	37.7 (204)	39.1 (138)		0.023	0.004
SLICC/ACR Damage Index scores at cohort entry, mean (SD)	1549	1.2 (1.8)	1.2 (1.7)	1.3 (1.8)	1.3 (1.7)	0.448		0.116

* Serology was not collected for all patients; for some it was only recorded whether or not patients had met the immunologic criterion for SLE, or included in SLEDAI scores. SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; SLAM-R: revised Systemic Lupus Activity Measure; PGA: physician's global assessment; VAS: visual analog scale; SLAQ: Systemic Lupus Activity Questionnaire; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; MCS: mental component summary; ACR: American College of Rheumatology; SLICC: Systemic Lupus International Collaborating Clinics; ANA: antinuclear antibody; aPL: antiphospholipid antibodies.

Table 3. Treatment (at cohort entry).

Treatment	N	Disease Activity				P Values for Between-group Differences	
		Low	Moderate	Moderately High	Very High	Chi-square Test	Test for Trend
Prednisone	1777	41.8	45.4	46.1	64.1	**< 0.001**	**< 0.001**
Daily prednisone dose*, mean (SD)	605	11 (11)	11.7 (13.2)	13.0 (12.4)	24.3 (38.5)	**0.001**	
> 7.5 mg/day*	605	12.7	15.0	15.0	31.5		**< 0.001**
Antimalarials	1777	65.3	68.5	68.7	70.9	0.38	0.094
Immunosuppressants							
Azathioprine	1777	16.2	20.1	16.4	22.5	0.071	0.087
Mycophenolate	1777	6.9	9.2	9.3	9.9	0.28	0.072
Cyclophosphamide	1777	1.0	1.4	1.5	5.7	**< 0.001**	**< 0.001**
Methotrexate	1777	5.8	8.3	8.8	6.5	0.206	0.27
Leflunomide	1777	0.1	0.6	0	0	0.205	0.524
Cyclosporine	1777	0.6	0.3	0.5	0.4	0.867	0.598
Rituximab	1777	0.1	0.6	0	0.4	0.336	0.767
Any immunosuppressant, excluding prednisone †	1777	29.7	37.9	35.5	44.3	**< 0.001**	**< 0.001**

Values are % unless otherwise specified. * Prednisone dose available only for a subset of patients. † A small no. patients were taking > 1 immunosuppressant; therefore, total frequency of patients taking individual medications is greater than proportion on any immunosuppressant. Values in bold face are statistically significant.

Table 4. Transition matrices: probabilities of transitioning between different categories of disease activity over 2 consecutive visits, based on SLEDAI-2K score*.

From cohort entry to 1 year later, n = 1200					
		Year 1			
	SLEDAI Group	Low	Moderate	Moderately High	Very High
Cohort entry	Low	70.9	15.6	9.0	4.5
	Moderate	36.3	32.3	20.2	11.3
	Moderately high	30.7	24.1	32.9	12.2
	Very high	19.4	15.3	29.5	35.9
From Year 1 to Year 2 of followup, n = 425					
		Year 2			
	SLEDAI Group	Low	Moderate	Moderately High	Very High
Year 1	Low	67.3	14.1	12.7	5.9
	Moderate	53.9	23.0	13.0	10.0
	Moderately high	35.1	17.7	35.1	12.1
	Very high	22.7	22.7	30.6	24.1
From Year 2 to Year 3 of followup, n = 220					
		Year 3			
	SLEDAI Group	Low	Moderate	Moderately High	Very High
Year 2	Low	58.2	16.0	19.3	6.5
	Moderate	38.3	36.1	14.9	10.7
	Moderately high	33.3	15.7	39.2	11.8
	Very high	17.3	13.9	34.4	34.4
From Year 3 to Year 4 of followup, n = 154					
		Year 4			
	SLEDAI Group	Low	Moderate	Moderately High	Very High
Year 3	Low	52.7	33.3	12.3	1.7
	Moderate	45.7	17.1	31.5	5.8
	Moderately high	18.5	23.8	42.1	15.7
	Very high	12.5	16.7	33.3	37.5
From Year 4 to Year 5 of followup, n = 106					
		Year 5			
	SLEDAI Group	Low	Moderate	Moderately High	Very High
Year 4	Low	52.7	27.8	16.7	2.7
	Moderate	36.0	44.0	11.9	8.0
	Moderately high	22.2	19.5	47.2	11.2
	Very high	11.2	11.2	22.2	55.5

* Decreasing patient followup data available each year. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

while not taking corticosteroids[36]. These results emphasize the difficulty SLE clinicians and their patients experience in maintaining persistent control of disease.

We found that a higher SLEDAI score was the best predictor of high disease activity in subsequent years, in both linear and more complex mixed model multivariate analyses. No clinical or treatment variables (e.g., nephritis or immunosuppressive treatment) predicted longitudinal disease activity. Among demographic variables, only higher income was independently associated with lower disease activity at subsequent visits. The better longterm evolution of SLE disease activity for patients with higher income might be partly explained by their better access to care. Indeed, the proportion of patients reporting additional private insurance coverage for prescription drugs increased from 38.1% in the lowest income group to 88.6% in the highest income group ($p < 0.0001$). Similarly, at cohort entry, 84.7% of patients in the highest income group reported having no problem with the cost of their SLE medications compared to only 49.6% in the lowest income group ($p < 0.0001$). This finding has not been previously reported, although a multinational study found lower disease activity in countries with higher national social wealth[37]. In addition, Alarcon, *et al* reported that poverty was predictive of higher disease activity, especially among African Americans[38]. Lower incomes or socioeconomic status have been previously associated with increased damage accrual[39,40,41,42], including in this cohort[16]. We had previously also found that lower educational attainment was associated with higher disease activity in this same cohort in cross-sectional analysis[43]. The relationship between socio-

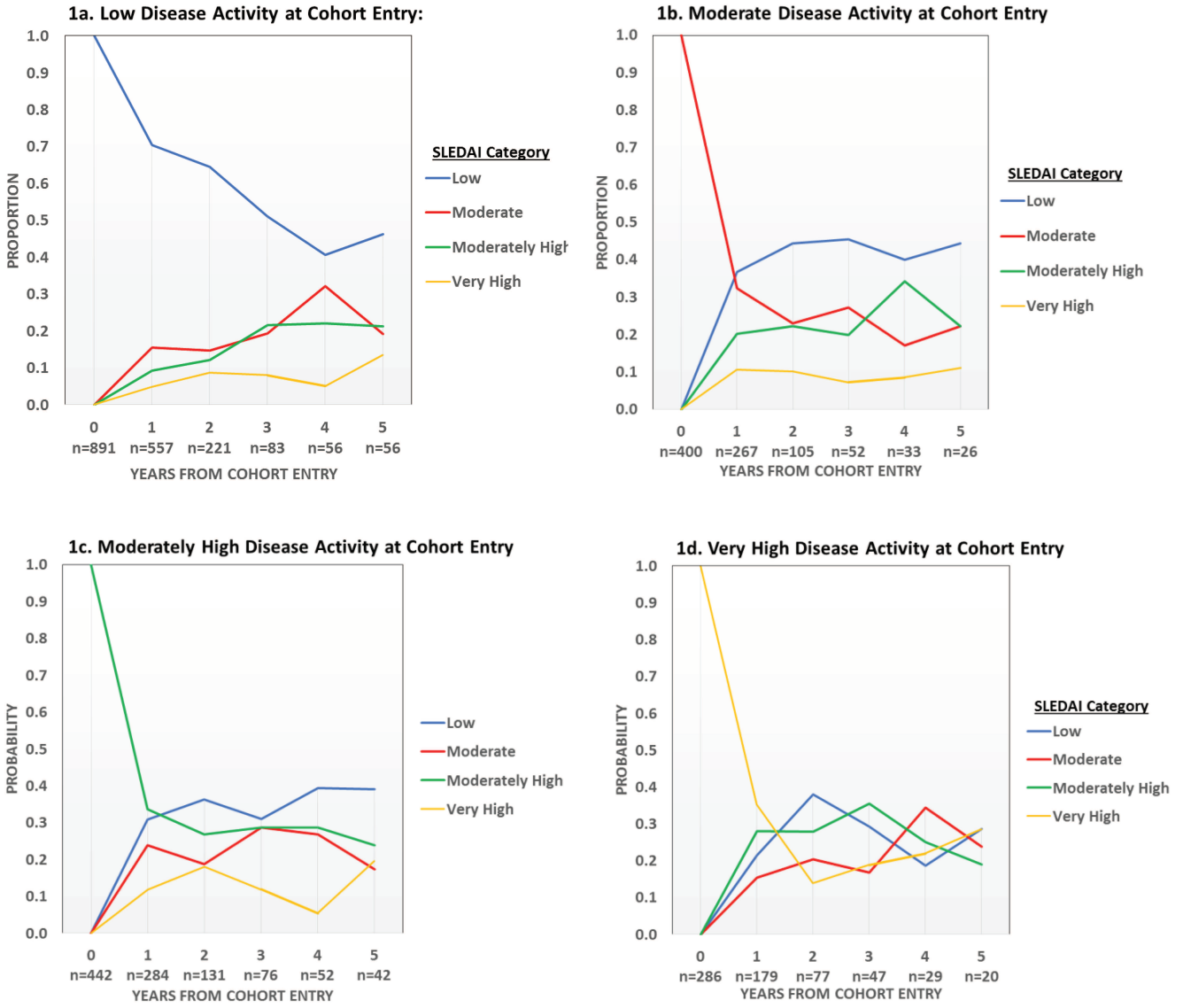

Figure 1. Proportions (y-axis) of patients transitioning to specific disease activity groups across followup time (x-axis), depending on disease activity at cohort entry. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

economic status and SLE is not well understood, although it has become clear that the effect goes beyond access to care[44]. Because damage is thought to accrue from ongoing active disease as well as treatment, our findings most likely reflect a higher burden of disease experienced by those with lower incomes, but may also reflect better access to care. We were not, however, able to measure whether income had any effect on treatment delays or adherence in this cohort. No other demographic variables were predictive.

Persistent disease activity despite standard of care therapy is an important theme in SLE research and clinical care. Previous studies have shown that persistent disease activity is associated with increased damage accrual[4,45,46]. Gilboe, *et al* reported that higher disease activity early in the disease course predicts later active disease and damage[45], and in another inception cohort, 25% of patients failed to achieve low disease activity within the first year; almost half of these continued to have persistent active disease throughout the 5-year followup period[4]. This points to our lack of ability to achieve sustained low disease activity or clinical remission, resulting in a combination of ongoing disease activity and damage accrual over time. Zen, *et al* recently found that a sustained 2-year remission was the minimal duration of remission associated with reduced damage[46], emphasizing the need for more prolonged disease control to improve outcomes.

Table 5. Multivariable linear regression analysis of changes in disease activity in the first year after cohort entry*.

Variables	Estimate	Standard Error	T Statistics	p
Intercept	1.05	0.20	5.23	< 0.001
Disease duration	–0.005	0.002	–2.4	0.020
Income†, annually				
$15,000–$29,999	–0.06	0.07	–1.53	0.361
$30,000–$49,999	–0.11	0.07	–1.53	0.132
≥ $50,000	–0.26	0.09	–2.88	0.015
ANA	–0.26	0.15	–1.75	0.104
Cohort entry SLEDAI-2K	0.07	0.004	16.28	< 0.001
Sex	0.15	0.07	–2.41	0.057
Arthritis	0.10	0.05	2.00	0.049

* Quantitative SLEDAI-2K scores rather than the 4 groups of disease activity were used to increase precision.
† Reference category income < Can$15,000. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ANA: antinuclear antibody.

There are a number of limitations to this study. While the data were collected prospectively, patients entered the cohort at a mean of 11 years of disease, meaning that we had no information on disease activity earlier in their disease course. In addition, data were collected annually; this makes it possible that disease activity was underestimated (because flares may have occurred between annual visits) and direct correlations between disease activity and treatment decisions are difficult. Conversely, it is also possible that patients with low disease activity were more likely to be lost to followup, resulting in an overestimation of disease activity. Nonetheless, this cohort is large, multiethnic, and extends across Canada, with rigorously collected data, thus providing reliable, generalizable results.

Investigators had begun previously to define low disease activity in SLE, with development of the Lupus Low Disease Activity State (LLDAS), analogous to the low disease activity target long in use for rheumatoid arthritis[47]. LLDAS was defined as a SLEDAI ≤ 4, no new SLE activity compared to previous visit, prednisone dosage ≤ 7.5 mg/day, Safety of Estrogens in Lupus Erythematosus: National Assessment–SLEDAI PGA ≤ 1, and standard, well-tolerated doses of immunosuppressant and biologics. Although our dataset does not have all the elements needed to determine LLDAS (i.e., doses and tolerability of immunosuppressives), we do collect several of these elements. In our cohort, only half of the patients had a SLEDAI < 4 at cohort entry, and even in those patients it was generally not sustained, with about 30–40% probability of increased disease activity at subsequent visits (Table 4). Further, in a subset analysis, more than 15% of patients with SLEDAI < 4 were taking ≥ 7.5 mg/day of prednisone. Thus, only a small proportion of our cohort would meet the criteria for sustained LLDAS.

Glucocorticoids, most commonly prednisone, continue to be the "go-to" medication for both disease flares and active disease unresponsive to other therapies. This is not because clinicians fail to recognize the overwhelming evidence for the risk of damage from cumulative prednisone dosing[5,48,49], but because of lack of effective therapeutic alternatives[1,8,50]. Our data, similar to others', suggest that optimal control of disease activity is often not achieved with available steroid- sparing treatment options, with more than half of patients taking prednisone, often at substantial doses. This highlights gaps in the optimal treatment of SLE and the need for additional therapies.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. Arthritis Res Ther 2012;14 Suppl 4:S4.
2. Pego-Reigosa JM, Rua-Figueroa I, Lopez-Longo FJ, Galindo-Izquierdo M, Calvo-Alen J, Olive-Marques A, et al; RELESSER Group, from the Spanish Society of Rheumatology Systemic Autoimmune Diseases Study Group (EASSER). Analysis of disease activity and response to treatment in a large Spanish cohort of patients with systemic lupus erythematosus. Lupus 2015;24:720-9.
3. Nossent J, Cikes N, Kiss E, Marchesoni A, Nassonova V, Mosca M, et al. Current causes of death in systemic lupus erythematosus in Europe, 2000—2004: relation to disease activity and damage accrual. Lupus 2007;16:309-17.
4. Nossent J, Kiss E, Rozman B, Pokorny G, Vlachoyiannopoulos P, Olesinska M, et al. Disease activity and damage accrual during the early disease course in a multinational inception cohort of patients with systemic lupus erythematosus. Lupus 2010;19:949-56.
5. Al Sawah S, Zhang X, Zhu B, Magder LS, Foster SA, Iikuni N, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins Lupus Cohort. Lupus Sci Med 2015;2:e000066.
6. Bruce IN, O'Keeffe AG, Farewell V, Hanly JG, Manzi S, Su L, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International

Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis 2015;74:1706-13.
7. Steiman AJ, Urowitz MB, Ibanez D, Papneja A, Gladman DD. Prolonged clinical remission in patients with systemic lupus erythematosus. J Rheumatol 2014;41:1808-16.
8. Lazaro E, Scherlinger M, Truchetet ME, Chiche L, Schaeverbeke T, Blanco P, et al. Biotherapies in systemic lupus erythematosus: new targets. Joint Bone Spine 2017;84:267-74.
9. Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheum 2014;66:379-89.
10. Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D'Cruz D, Wallace DJ, et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:3077-87.
11. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010;62:222-33.
12. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al; LUNAR Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215-26.
13. Clowse ME, Wallace DJ, Furie RA, Petri MA, Pike MC, Leszczynski P, et al. Efficacy and safety of epratuzumab in moderately to severely active systemic lupus erythematosus: results from two phase III randomized, double-blind, placebo-controlled trials. Arthritis Rheum 2017;69:362-75.
14. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum 2013;65:2368-79.
15. Nikpour M, Urowitz MB, Ibañez D, Gladman DD. Frequency and determinants of flare and persistently active disease in systemic lupus erythematosus. Arthritis Rheum 2009;61:1152-8.
16. Peschken CA, Katz SJ, Silverman E, Pope JE, Fortin PR, Pineau C, et al; Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus (CaNIOS). The 1000 Canadian faces of lupus: determinants of disease outcome in a large multiethnic cohort. J Rheumatol 2009;36:1200-8.
17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
18. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630-40.
19. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288-91.
20. Karlson EW, Daltroy LH, Rivest C, Ramsey-Goldman R, Wright EA, Partridge AJ, et al. Validation of a Systemic Lupus Activity Questionnaire (SLAQ) for population studies. Lupus 2003; 12:280-6.
21. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
22. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. Systemic lupus international collaborative clinics: development of a damage index in systemic lupus erythematosus. J Rheumatol 1992;19:1820-1.
23. Gladman DD, Urowitz MB, Goldsmith CH, Fortin P, Ginzler E, Gordon C, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:809-13.
24. Statistics Canada. 2001 census dictionary Internet version. [Internet. Accessed August 15, 2018.] Available from: www12.statcan.gc.ca/english/census01/Products/Reference/dict/index.htm
25. Abrahamowicz M, Fortin PR, du Berger R, Nayak V, Neville C, Liang MH. The relationship between disease activity and expert physician's decision to start major treatment in active systemic lupus erythematosus: a decision aid for development of entry criteria for clinical trials. J Rheumatol 1998;25:277-84.
26. Yee CS, Farewell VT, Isenberg DA, Griffiths B, Teh LS, Bruce IN, et al. The use of Systemic Lupus Erythematosus Disease Activity Index-2000 to define active disease and minimal clinically meaningful change based on data from a large cohort of systemic lupus erythematosus patients. Rheumatology 2011;50:982-8.
27. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974;19:716-23.
28. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011; 30:377-99.
29. Diggle PJ. An approach to the analysis of repeated measurements. Biometrics 1988;44:959-71.
30. Kleinbaum DG, Kupper L, Nizam A, Rosenberg E. Applied regression analysis and other multivariable methods. Boston: Cenngage Learning; 2014.
31. RStudio Team (2015). RStudio: Integrated Development for R. RStudio Inc., Boston, Massachusetts, USA. [Internet. Accessed August 23, 2018.] Available from: www.rstudio.com
32. Zhang J, Gonzalez LA, Roseman JM, Vila LM, Reveille JD, Alarcon GS. 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. Lupus 2010;19:727-33.
33. Závada J, Uher M, Svobodová R, Olejárová M, Hušáková M, Ciferská H, et al. Serum tenascin-C discriminates patients with active SLE from inactive patients and healthy controls and predicts the need to escalate immunosuppressive therapy: a cohort study. Arthritis Res Ther 2015;17:341.
34. Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, Medina JA, Moran MA, Ruiz-Irastorza G. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. Rheumatology 2014;53:1470-6.
35. Barr SG, Zonana-Nacach A, Magder LS, Petri M. Patterns of disease activity in systemic lupus erythematosus. Arthritis Rheum 1999;42:2682-8.
36. Zen M, Iaccarino L, Gatto M, Bettio S, Nalotto L, Ghirardello A, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. Ann Rheum Dis 2015;74:2117-22.
37. Golder V, Kandane-Rathnayake R, Hoi AY, Huq M, Louthrenoo W, An Y, et al. Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort. Arthritis Res Ther 2016;18:260.
38. Alarcon GS, McGwin G Jr, Sanchez ML, Bastian HM, Fessler BJ, Friedman AW, et al. Systemic lupus erythematosus in three ethnic groups. XIV. Poverty, wealth, and their influence on disease activity. Arthritis Rheum 2004;51:73-7.
39. Lotstein DS, Ward MM, Bush TM, Lambert RE, van Vollenhoven R, Neuwelt CM. Socioeconomic status and health in women with systemic lupus erythematosus. J Rheumatol 1998;25:1720-9.
40. Sutcliffe N, Clarke AE, Gordon C, Farewell V, Isenberg DA. The association of socio-economic status, race, psychosocial factors and

outcome in patients with systemic lupus erythematosus. Rheumatology 1999;38:1130-7.
41. Mendoza-Pinto C, Mendez-Martinez S, Soto-Santillan P, Galindo Herrera J, Perez-Contreras I, Macias-Diaz S, et al. Socioeconomic status and organ damage in Mexican systemic lupus erythematosus women. Lupus 2015;24:1227-32.
42. Petri M, Purvey S, Fang H, Magder LS. Predictors of organ damage in systemic lupus erythematosus: the Hopkins Lupus Cohort. Arthritis Rheum 2012;64:4021-8.
43. George A, Wong-Pak A, Peschken CA, Silverman E, Pineau C, Smith CD, et al; 1000 Canadian Faces of Lupus Investigators. Influence of education on disease activity and damage in systemic lupus erythematosus: data from the 1000 Canadian Faces of Lupus. Arthritis Care Res 2017;69:124-32.
44. Ward MM. Examining health disparities in systemic lupus erythematosus. Arthritis Rheum 2001;44:2711-4.
45. Gilboe IM, Kvien TK, Husby G. Disease course in systemic lupus erythematosus: changes in health status, disease activity, and organ damage after 2 years. J Rheumatol 2001;28:266-74.
46. Zen M, Iaccarino L, Gatto M, Bettio S, Saccon F, Ghirardello A, et al. The effect of different durations of remission on damage accrual: results from a prospective monocentric cohort of caucasian patients. Ann Rheum Dis 2017;76:562-5.
47. Franklyn K, Lau CS, Navarra SV, Louthrenoo W, Lateef A, Hamijoyo L, et al; Asia-Pacific Lupus Collaboration. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis 2016;75:1615-21.
48. Apostolopoulos D, Kandane-Rathnayake R, Raghunath S, Hoi A, Nikpour M, Morand EF. Independent association of glucocorticoids with damage accrual in SLE. Lupus Sci Med 2016;3:e000157.
49. Thamer M, Hernan MA, Zhang Y, Cotter D, Petri M. Prednisone, lupus activity, and permanent organ damage. J Rheumatol 2009;36:560-4.
50. Furie R, Toder K, Zapantis E. Lessons learned from the clinical trials of novel biologics and small molecules in lupus nephritis. Semin Nephrol 2015;35:509-20.