Prevalence of Flare and Influence of Demographic and Serologic Factors on Flare Risk in Systemic Lupus Erythematosus: A Prospective Study

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ABSTRACT. ***Objective.*** We determined the prevalence of and risk factors for British Isles Lupus Activity Group (BILAG) flare in patients with systemic lupus erythematosus (SLE).

Methods. We followed 299 patients for 1 year with the BILAG scores calculated using British Lupus Integrated Prospective System software and confirmed with manual calculation.

Results. "A" flares occurred at a rate of 0.254/year, "B" flares 1.637/year, and A or B flares 1.765/year. The most common A flares were renal and mucocutaneous. The most common B flares were hematologic, renal, mucocutaneous, and musculoskeletal. Risk factors for a later A or B flare in the hematological system included: low C3 ($p < 0.0001$), low C4 ($p = 0.0004$), and positive anti-double-stranded (ds)DNA ($p = 0.003$); in the mucocutaneous system: low C3 ($p = 0.02$) and low C4 ($p = 0.0004$); and in the renal system: low C3 ($p = 0.02$) and low C4 ($p = 0.02$). In a stepwise regression model, only ethnicity ($p = 0.02$) and low C4 ($p = 0.0002$) remained as independent predictors of later A or 2B flares.

Conclusion. The organ system distribution of A and B flares is very different, with A flares more common in renal and mucocutaneous, and B flares more common in hematologic and renal systems. A or 2B flares are significantly more common in African Americans and in patients with abnormal serologies (low C3, low C4, or high anti-dsDNA). If flare is an outcome in an SLE clinical trial, these factors must be balanced by taking them into account at baseline in terms of randomization, or by statistical adjustment in final analyses. (First Release Oct 15 2009; J Rheumatol 2009; 36:2476–80; doi:10.3899/jrheum.090019)

Key Indexing Terms:
LUPUS BRITISH ISLES LUPUS ASSESSMENT GROUP FLARE

There is no "gold standard" for measuring disease activity and/or flare in systemic lupus erythematosus (SLE). Many lupus activity indices have been developed and validated, including global scoring systems, such as the Systemic Lupus Activity Measurement (SLAM)[1-4], SLE Disease Activity Index (SLEDAI)[3,5-7], Lupus Activity Index (LAI)[8,9], European Consensus Lupus Activity Measurement (ECLAM)[3,10-12], and one that is organ-based, the British Isles Lupus Assessment Group (BILAG)[13]. All these indices have been shown to be valid, reliable, and sensitive to change[14-17].

BILAG, based on the physician's intent to treat, includes a total of 86 items in 8 organ systems: general, mucocutaneous, neurological, musculoskeletal, cardiovascular/respiratory, vasculitis, renal, and hematological. Scores of A, B, C, D, and E are calculated for each organ system, based upon whether clinical features are present and if they are new, worse, same, or improving in the last 4 weeks, compared with the previous visit. Scores can be calculated manually or by a computer program called the British Lupus Integrated Prospective System (BLIPS)[18].

A score of "A" in any organ system indicates very active lupus that is expected to be treated with new or an increased dose of corticosteroids (prednisolone > 20 mg per day or equivalent)[2]. A score of "B" indicates moderate activity that requires lower doses of corticosteroids, antimalarials, or nonsteroidal antiinflammatory drugs (NSAID). A score of "C" implies a mild or stable activity that requires only symptomatic treatment, such as analgesics and NSAID. A score of "D" is recorded if there are no current symptoms, but the organ system has been active previously. If the system has never been involved and there is no current disease activity, a score of "E" is recorded[2]. An active lupus flare is defined as a new A (severe flare) or B (moderate flare) score in at least one system that previously scored a C, D, or E[19].

The aim of our study was to determine the incidence of A and B organ flare, using BILAG, over 1 year, in a large

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cohort of well described patients with SLE in the United States. In addition, we determined the influence of demographic and serologic factors on risk of flare.

MATERIALS AND METHODS

We followed 299 patients with SLE prospectively for 1 year (303.1 total followup person-years). The study was approved by the Johns Hopkins University Institutional Review Board and all patients provided signed informed consent. At each quarterly visit, or more frequently if there were "interval" visits, clinical features that were part of the BILAG assessment of disease activity were recorded in the clinic on standardized BILAG encounter forms. Medications were not required to be stable during the study. The data gathered were subsequently entered into the BLIPS computer software (version 3) by research coordinators[18]. Using BLIPS software, the BILAG index was recorded for 8 organ systems (general, mucocutaneous, neurological, musculoskeletal, cardiovascular/respiratory, vasculitis, renal, and hematological)[15]. This index generates scores of A for severe activity and B for moderate activity. Patients whose scores moved to an A or to a B in any of the 8 organs/systems, preceded by a C/D/E activity score, were considered to have experienced flare. Each BLIPS result was checked by hand scoring. This was especially important in the renal system. If proteinuria increased from 1 to 2+ on the urine dipstick, the correct score using the BILAG manual was B. However, the BLIPS software gave an incorrect C score in this setting. The BILAG 2004, a revision of the classic BILAG, was not available at the time of this study[20].

C3 and C4 concentrations were measured using the Immage kit (Beckman). Anti-double-stranded (ds)DNA by Crithidia was tested first at 1:10 dilution and then titered out, up to 640. Baseline antinuclear antibodies (ANA) were not tested as part of the study.

Statistical analysis. The relevant demographic and laboratory variables were extracted from the Hopkins Lupus Cohort Access database using the Cohort ID as the unique identifier.

Statistical analysis was performed using Fisher's exact test for categorical variables and the Student t-test for continuous variables. A p value of 0.05 was taken as statistically significant.

RESULTS

The 299 patients with SLE had a mean age of 47 years and 88% were female. Caucasians represented 57% of the study population, followed by African Americans (37%), Asians (3%), Hispanics (2%), and other ethnicities (1%). The patients had 14.0 (± 2.8) mean years of education, 12.5 years (± 8.5) disease duration of SLE, 43.5% smoking (ever), 23.3% low C3, 22.3% low C4, and 25.5% were anti-dsDNA-positive. Cumulative American College of Rheumatology criteria included 54% malar rash, 20% discoid rash, 53% photosensitivity, 52% oral ulcers, 79% arthritis, 46% pleuritis, 25% pericarditis, 44% proteinuria, 7% seizures, 3% psychosis, 9% hemolytic anemia, 52% leukopenia, 53% lymphopenia, 27% thrombocytopenia, 63% anti-dsDNA, 14% anti-Sm, 68% antiphospholipid antibodies, and 97% positive ANA.

The prevalence of A, B, or A/B flares per year is shown in Table 1. Total years of followup were 303.07 for the 299 patients. The frequency of A flare was 0.254/year, B flare 1.637/year, and A or B flare 1.765/year. Seventeen percent of patients had an A flare and 69% had a B flare during the year of followup. Seventy percent had either an A or B flare. Considering the 8 organ systems separately, the most frequent A flare was seen in the renal system (0.102/yr) and the most frequent B flare in the hematologic system (0.868/yr), closely followed by the renal system (0.469/yr). The most frequent A or B flares per year, by organ system, were seen in the hematologic system (0.901/yr), followed by the renal system (0.571/yr).

Table 1. Frequency of BILAG A, B, or A/B flares by organ system, per person-year.

Organ System	A	B	A or B	Two B Flares
Any organ	0.254	1.637	1.765	0.502
General	0.000	0.016	0.016	
Mucocutaneous	0.059	0.370	0.429	
Neurologic	0.023	0.016	0.040	
Musculoskeletal	0.013	0.313	0.327	
Cardiorespiratory	0.003	0.030	0.033	
Vasculitis	0.030	0.046	0.076	
Renal	0.102	0.469	0.571	
Hematologic	0.033	0.868	0.901	

BILAG: British Isles Lupus Assessment Group index.

The frequency of 2B flares (flares in which 2 organs have scored a B at the same visit) was 0.5/year. The most frequent combinations leading to 2B flares were renal and hematologic (0.165/yr), followed by musculoskeletal and hematologic (0.076/yr) and mucocutaneous and hematologic (0.053/yr).

Table 2 shows the distribution summary of how a subject progressed to the A (severe) category from a previous score of B, C, D, or E, or to a B category from a previous score of C, D, or E. For mucocutaneous flares, most A flares were preceded by a B score at the previous visit. For renal A flares, the previous score was equally an E or a C. A hematologic flares were always preceded by a score of B.

Flares occurred equally throughout the year: 27% at 3 months, 24% between 3 and 6 months, 25% between 6 and 9 months, and 24% between 9 and 12 months. Not all flares resulted in a treatment change.

Table 3 represents various risk factors leading to later A or B flares, based upon the individual organ systems. Women and African Americans were more likely to have a flare than men or non-African Americans, respectively. Abnormal serologies were predictors of having a flare over the next year. Abnormal serologies were predictive of flares in the mucocutaneous, renal, and hematologic organ systems, but not the other organ systems.

Factors predictive of an A or 2B flare are shown in Table 4. African American ethnicity, low C3, low C4, or anti-dsDNA were all predictive.

Table 5 shows the multiple variable model for an A or 2B flare. The best regression model contained African American ethnicity, low C3, low C4, and anti-dsDNA. Age ≥ 45 years (vs younger) did not affect the frequency of A or B flares. Duration of SLE ≥ 10 years (vs less) also did not affect the frequency of BILAG flares. Prednisone use at

Table 2. Distribution summary of progression to A or B flares from previous BILAG score of E, D, C, or B. Each cell shows the number of patients.

Organ Systems	E→A	D→A	C→A	B→A	E→B	D→B	C→B
General	0	0	0	0	4	0	1
Mucocutaneous	2	1	1	7	28	19	17
Neurologic	4	2	0	1	5	0	0
Musculoskeletal	1	0	0	3	19	14	26
Cardiorespiratory	0	0	0	1	3	1	0
Vasculitis	1	0	1	2	5	1	2
Renal	4	2	6	10	26	10	38
Hematologic	0	0	0	8	13	17	37

BILAG: British Isles Lupus Assessment Group index.

Table 3. Risk factors for later A or B flares based on organ system involvement.

Factor at Baseline	Organ System	No A or B Flare, %	Later A or B Flare, %	p	OR (95% CI)
Sex female	Hematologic	85	96	0.0100	3.85 (1.41, 10.6)
	Any flare	83	91	0.0394	2.13 (1.06, 4.29)
Ethnicity African American	Hematologic	34	52	0.0070	2.07 (1.23, 3.50)
	Any flare	25	47	0.0003	2.67 (1.57, 4.55)
Low C3	Mucocutaneous	20	36	0.0156	2.20 (1.18, 4.10)
	Renal	19	33	0.0217	2.02 (1.14, 3.57)
	Hematologic	17	39	< 0.0001	3.19 (1.80, 5.63)
	Any flare	17	27	0.0580	1.87 (1.01, 3.46)
Low C4	Mucocutaneous	18	41	0.0004	3.14 (1.69, 5.84)
	Renal	19	31	0.0217	1.98 (1.11, 3.51)
	Hematologic	17	36	0.0004	2.89 (1.63, 5.13)
	Any flare	15	27	0.0183	2.17 (1.15, 4.11)
Anti-dsDNA-positive	Hematologic	20	37	0.0033	2.33 (1.34, 4.04)
	Any flare	19	29	0.0651	1.80 (1.00, 3.26)
Low C3 AND anti-dsDNA-positive	Mucocutaneous	10	23	0.0095	2.71 (1.30, 5.67)
	Renal	8	23	0.0017	3.23 (1.60, 6.54)
	Hematologic	10	20	0.0209	2.40 (1.19, 4.84)
	Any flare	7	16	0.02770	2.61 (1.10, 6.18)
Low C4 AND anti-dsDNA-positive	Mucocutaneous	8	25	0.0009	3.91 (1.83, 8.33)
	Renal	8	18	0.0249	2.45 (1.18, 5.12)
	Hematologic	8	20	0.0026	3.13 (1.50, 6.54)
	Any flare	5	15	0.0110	3.47 (1.30, 9.30)
Low C3 AND low C4	Mucocutaneous	10	27	0.0024	3.18 (1.56, 6.48)
	Hematologic	9	25	0.0007	3.37 (1.70, 6.68)
	Any flare	7	18	0.0120	2.98 (1.27, 7.00)

baseline was associated with the frequency of A flare (p = 0.0057), B flare (p = 0.0004), and A or B flare (p = 0.004). Hydroxychloroquine use at baseline did not affect the frequency of A, B, or A or B flares. Immunosuppressive drug use at baseline was associated with A flares (p = 0.0011), B flares (p = 0.0006), or A or B flares (p = 0.0021).

DISCUSSION

Ours is the first study of the prevalence of BILAG A or B flares in a US population. The previous study conducted in the United Kingdom found that over 1 year, 10.4% had an A flare and 51% had a B flare, compared with 17% with an A and 69% with a B flare in our study. The higher frequency of flare in our study may reflect differences in ethnicity, including renal flares in our African American patients.

This is the first study of the pattern of progression, by organ system, to an A or B flare. We found that the progression pattern differs by organ system and by A or B flare. For example, most A flares were preceded by a B score, with the exception of the neurologic and renal systems. In contrast, B flares could be preceded by E, D, or C scores, with the exception of the neurologic system, in which B flares were preceded by E scores.

Several recent clinical trials have based enrollment on one A or two B flares. We were very interested in the combination of organ systems that most frequently constituted a

Table 4. Influence of demographic and serologic factors in BILAG A or 2B flare.

Factor at Baseline	No A or 2B, %	Later A or 2B, %	p	OR (95% CI)
African American	35	49	0.0397	1.77 (1.04, 3.01)
Low C3	18	36	0.0019	2.57 (1.45, 4.55)
Low C4	17	36	0.0009	2.75 (1.54, 4.90)
Anti-dsDNA-positive	21	37	0.0070	2.24 (1.28, 3.92)

BILAG: British Isles Lupus Assessment Group index.

Table 5. Multiple regression model of later A or 2B flare.

Factor	Estimate	SE	Chi-square	p
Intercept	0.512	0.166	9.54	0.0020
Low C4	0.535	0.166	10.39	0.0013
Ethnicity	0.343	0.145	5.62	0.0178
Anti-dsDNA	0.282	0.162	3.03	0.0817

dsDNA: double-stranded DNA.

2B flare. Each of the 3 most common combinations included the hematologic system, with the hematologic B score usually not requiring treatment. Thus, our data show that two B flares may not always have the same severity, or need for aggressive treatment, as one A flare.

The BILAG was designed to reflect the physician's intention to treat. However, physicians differ in the treatment of SLE. We try to minimize exposure to corticosteroids. Some flares may resolve spontaneously, or in response to a brief burst of intramuscular corticosteroid, as proven in the FLOAT trial[21]. Some B flares, especially hematologic and cutaneous, may not require treatment. Treatment of disease activity may have been started at a previous visit for the renal, skin, and hematologic organ systems, but the treatment may require time to be efficacious. Thus, it is not surprising that not all A and B flares require treatment. Indeed, the original analysis of flares by the BILAG group showed that there was a significant difference in the frequency and management of A flares (new, very active flare) compared with B flares (new, moderate flare) and in treatment by organ[19]. In the British series, only 20% of neurologic A flares and 17% of vasculitis A flares were treated. Only 41% of B flares required an increase in therapy.

This is the first study of demographic and serologic predictors of flares, ascertained using the BILAG, in a US population. Women were more likely to have a flare than men. Although we found that men had fewer flares, some studies have shown that men have a more severe course of lupus[22]. African Americans were more likely to experience flare overall and in the hematologic system than non-African Americans. The increased risk of renal lupus in African Americans is well known[23], but this is the first proof of an overall increase in flares.

The role of serologies in predicting flares has been controversial. In a previous study, using multiple different definitions of flare, we showed that no serology predicted which patient would have a flare the next month[24,25]. However, on the actual day of the flare, anti-dsDNA was lower in the serum (likely representing deposition of anti-dsDNA immune complexes in tissues) and complement was lower with renal or hematologic flares.

Our current study extends those results in BILAG-defined organ system flares. Both low C3 and low C4 doubled the risk of mucocutaneous, renal, or hematologic flares over the next year. Surprisingly, anti-dsDNA was only predictive of hematologic or "any" organ flare over the next year. Because our study examined anti-dsDNA only by the Crithidia assay, the Farr or ELISA might have given different results. Several clinical trials have suggested that treatment of serologic abnormalities can reduce flares. For example, treatment of a change in serologies may reduce later disease activity[26]. Treatment of anti-dsDNA changes may reduce flares[27,28]. In addition, a reduction of anti-dsDNA led to a reduction of later flares[29].

In conclusion, the BILAG system of flare scores offers the advantage of analysis both by severity, by A or B score, and by organ system. The natural history of BILAG flares elucidated in our study indicates that the progression to an A or B flare differs, and that progression also differs by organ system. The hematologic B flare often does not require treatment and should not be allowed as an entry criterion for clinical trials of major immunosuppressive regimens. In the multiple regression models, the 2 factors that remained independent predictors of later flares were ethnicity and low C4 concentration. These factors must now be taken into account in the design and analysis of clinical trials that include flare as an outcome measure.

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