Flares in Pediatric Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the flare rate and the change in Safety of Estrogens in Lupus Erythematosus: National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI) score with disease flare in pediatric systemic lupus erythematosus (pSLE).

Methods. A retrospective chart review of 62 patients with pSLE (ages 5–20 yrs). A flare was defined as the start of, or increase in, the dose of corticosteroids and/or the addition of an immunosuppressive medication. All pre-flare, flare, and post-flare visits were recorded with a SELENA SLEDAI score calculated for each visit. The flare rate was calculated by dividing the total number of flares in the cohort by the total followup years.

Results. Sixty-two patients were eligible. Forty-seven patients had 112 flares. The average number of flares/patient was 1.8 ± 2.0 and the mean inter-flare time was 15.4 ± 17.9 months. The flare rate in pSLE was 0.46 flares/patient-year of followup. The median time to first flare from the date of diagnosis was 14.3 months. Patients with cytopenia, pleuritis, or pericarditis, or a positive antibody to Smith nuclear antigen at the time of diagnosis had a significantly higher flare rate than those who did not. The average SELENA SLEDAI score at presentation was 12.5 ± 5.4, at the pre-flare visit 6.3 ± 3.5, and during a flare 7.9 ± 5.1.

Conclusion. This is the first large study to report a flare rate (0.46 flares/patient-year of followup) in pSLE. The flare rate was similar to what has been reported in pSLE previously but significantly lower than that reported in adults with lupus. The average change in the SELENA SLEDAI score with disease flare is 2 points. (First Release May 1 2007; J Rheumatol 2007;34:1341–4)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
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FLARE RATE

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease characterized by periods of fluctuating disease activity. Increases in SLE disease activity are classified as flares. Flares are an integral part of treating a patient with SLE, yet a universal definition of a flare does not exist for either the pediatric or the adult SLE patient[1]. Definitions of flare reported in the literature have been as varied as clinical signs of active disease and worsening laboratory measures, the introduction of and/or change in medication, change in the physician's global assessment (PGA), or as "flare" as recorded in the chart[1-8]. Even quantitative indices of disease activity such as the SLE Disease Activity Index (SLEDAI) do not adequately define a flare, as disease activity measures are meant to be only part of a patient's evaluation[9].

We undertook a retrospective study to determine the flare rate in pSLE using a definition of flare that incorporated the addition of or changes in medication. Based on this definition, the changes in the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) SLEDAI score with disease flare was calculated[10].

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MATERIALS AND METHODS

Patients/assessment. Eligible patients from the pediatric rheumatology clinic at Schneider Children's Hospital, New Hyde Park, New York, who fulfilled 4 of the 11 revised American College of Rheumatology (ACR) criteria for the classification of SLE[11] and had disease duration of 12 months or longer were included. For the purpose of our study, the date of disease onset was considered to be the visit where the patient met 4 of the 11 criteria for the classification of SLE. Patients were excluded if they were (1) diagnosed at an outside institution and treated with corticosteroids for more than 4 weeks prior to presentation in our office, (2) had no chart available for review, or (3) had a diagnosis of drug-induced lupus. Patients were evaluated retrospectively by clinical chart review by a single reviewer (JW) and data were entered into an Excel spreadsheet. All clinic visits, as well as summaries and laboratory data from hospital admissions, were reviewed to ensure that no flares were missed. Patient demographics, visit dates, classification criteria, medications used, SELENA SLEDAI score (calculated retrospectively), laboratory data including autoantibodies, complete blood counts, and urinalysis were recorded at the pre-flare, flare, and post-flare visits. Antinuclear antibody (ANA), anti-double-stranded DNA (dsDNA), C3, C4, and anti-Smith/RNP results were considered abnormal using the standards of the given laboratory.

Definition of flare. Disease flare was defined as: (1) the addition of, or increase in the dose of corticosteroids; and/or (2) the addition of an immunosuppressive medication (cyclophosphamide, cyclosporine, azathioprine, or mycophenolate mofetil) within 2 weeks of the prior office visit. If an immunosuppressive medication was added as a steroid-sparing agent, and not because of active disease, then that visit was not considered a flare visit. The office visit prior to the visit when the patient flared is the pre-flare visit. The post-flare visit is defined as the visit where the physician assessment read

"resolution of flare" or "stable" after a minimum of 2 weeks without defined flare.

Instruments. The SELENA SLEDAI is a refined SLEDAI that measures ongoing, recurrent, or initial events within 10 days of the office visit[9,10]. It is a weighted measure of disease activity of 24 items grouped into 9 organ systems. Critical organ system involvement is weighted highest. The score ranges from 0 (no activity) to 105 (maximum activity)[9]. If there was insufficient information from the patient's chart regarding the SLEDAI descriptors, the score was not calculated.

Statistical analysis. Univariate comparisons between sex, race, and other group variables were carried out using the Mann-Whitney/Kruskal-Wallis tests or Fisher's exact test, as appropriate, for continuous variables and categorical variables, respectively. Quartile estimates of time to first flare after initial diagnosis were calculated using the product-limit method (Kaplan-Meier) and comparisons were carried out using the log-rank test.

The flare rate was calculated by dividing the total number of flares by the total followup years. The calculated flare rate for our study was compared with the published adult flare rate using the incidence density ratio (IDR) method, under the weak assumption that the likelihood of a flare in a patient remains constant over the entire followup period. The IDR method is essentially based on a goodness-of-fit test[12].

All statistical analyses using the SELENA SLEDAI score were based on the first 5 flare sequences with exclusion of the first visit. A flare sequence consists of a pre-flare, flare, and post-flare visit. All missing data were treated as missing completely at random. No imputation methods were applied to estimate the missing values. All analyses were carried out using the SAS statistical software (SAS Institute, Cary, NC, USA).

The sample size for our study was limited to patients who met the inclusion criteria and had charts available for review during the specified study period. This study was not based on any formal power calculations.

RESULTS

Patients. Sixty-two of 73 patients with pSLE (53 female) followed by our division between 1984 and 2002 were eligible for the study. Eleven patients were excluded because they were diagnosed at an outside institution and treated with prednisone for more than 4 weeks prior to presenting to our office. Patients (Table 1) were followed on average for 4.0 + 2.7 years (range 1–11). There was a total of 246.1 patient followup years. The cohort's criteria for the classification of SLE are listed in Table 2.

Disease flare. Following the initial visit, 47 patients had a total of 112 disease flares. Twenty-six patients had more than 1 flare and 14 patients had 3 or more flares. The average number of flares per patient was 1.8 ± 1.98 (range 0–9). Thirty-two flares resulted in an increase in the oral corticosteroid dose, 29 flares were treated with pulse methylprednisolone, and 4 flares were treated with oral corticosteroids plus pulse methylprednisolone. Of the patients requiring an increase in oral corticosteroids, 15 were started on a dose ≤ 1 mg/kg/day and 17 patients were increased to a dose ≤ 2 mg/kg/day.

Table 1. Age at diagnosis (yrs) in pSLE (n = 62).

Patient Group	Mean (SD)
Overall (range 5–20)	12.8 (3.2)
Caucasians†	13.7 (2.4)
Non-Caucasians†	11.7 (3.7)
Male††	13.2 (4.2)
Female††	12.8 (3.0)

SD: standard deviation. † Significant difference $p < 0.02$; †† no significant difference.

Table 2. Criteria for classification of SLE at diagnosis in order of frequency (n = 62).

Classification Criteria	n (%)
Positive ANA	62 (100)
Autoantibodies	59 (95)
Arthritis	38 (61)
Cytopenia	38 (61)
Malar rash	30 (48)
Oral/nasal ulcerations	22 (35)
Nephritis	17 (27)
Proteinuria	15 (24)
Urinary casts	5 (8)
Discoid rash	10 (16)
Photosensitive rash	7 (11)
Pleuritis/pericarditis	5 (8)
Encephalopathy	2 (3)
Seizure	1 (2)
Psychosis	1 (2)

The flare rates are reported in Table 3. The median time to first flare was 14.3 months [95% confidence interval (95% CI) 10.1, 21.3] after diagnosis. The mean inter-flare time was 15.4 ± 17.9 months (median 9.9). The average length of time from the pre-flare to flare visit was 2.7 ± 4.0 months and the average length of time from the flare visit to the post-flare visit (or flare resolution) was 2.1 ± 1.9 months.

Based on the ACR classification criteria, patients who presented with cytopenia ($p < 0.01$), pleuritis or pericarditis ($p < 0.01$), or a positive antibody to Smith nuclear antigen ($p < 0.03$) had a significantly higher flare rate than those who did not. A significantly higher flare rate was also found in patients who presented with hematuria ($p < 0.03$), a low C3 ($p < 0.02$), an elevated erythrocyte sedimentation rate ($p < 0.03$), or anemia ($p < 0.002$), or in patients who required pulse methylprednisolone therapy ($p < 0.004$) or intravenous immunoglobulin at the time of diagnosis ($p < 0.001$).

Patients who presented with anemia were more likely to flare earlier than those who did not (10.2 mo vs 17.9 mo; $p < 0.02$). Patients with a positive antibody to Smith nuclear antigen tended to have an earlier time to first flare compared to

Table 3. Flare rates in pSLE (n = 47).

	Flare Rate	95% CI
Overall	0.46 (112/246.1)	0.37, 0.54
Males††	0.34 (14/40.95)	0.16, 0.52
Females††	0.48 (98/205.2)	0.38, 0.57
Caucasians†	0.35 (47/134.8)	0.25, 0.45
Non-Caucasians†	0.58 (65/111.27)	0.44, 0.73

† Significant difference $p < 0.01$; †† no significant difference.

those without the antibody; however, the difference was not statistically significant (13.9 mo vs 30.3 mo; p = 0.05). Those patients that required pulse methylprednisolone therapy at the time of diagnosis were likely to flare earlier in their disease course than those who did not (8.3 mo vs 17.6 mo; p < 0.02). Patients with anemia were more than twice as likely to flare compared to those patients without anemia (hazard ratio 2.2, 95% CI 1.2, 4.0).

SELENA SLEDAI. The average SELENA SLEDAI score at diagnosis was 12.5 + 5.4 (range 3–31). There was no significant difference in the SELENA SLEDAI score between males and females and Caucasians and non-Caucasians. The average SELENA SLEDAI during disease flare was 7.9 ± 5.1. Pre- and post-flare scores are reported in Table 4. SLEDAI scores were calculated for over 60% of flare visits; those missing were largely due to absent laboratory data.

DISCUSSION

An integral part of treating patients with SLE is to try to keep the frequency and intensity of flares to a minimum. Flares increase organ system damage and necessitate increases in medication resulting in significant side effects. Studies on flares in pSLE have been mainly confined to small case series and there is no large series such as ours that has reported a flare rate in pSLE.

Our flare rate of 0.46 flares per patient-year of followup was similar to 2 other studies that reported on flare rates in pSLE[5,6]. Merino, *et al* reported a flare rate of 0.54 flares per patient-year of followup in 11 children (8 female) with SLE[5]. The patients' average age at study entry was 14.7 ± 2.5 years (range 11–19). Flare was defined as an increase in the PGA from the prior visit. Flares were attributed to worsening malar rash, cutaneous vasculitis, and recurrent or worsening renal involvement[5]. Tanaka, *et al* reported a flare rate of 0.61 flares per patient-year of followup (15 flares/24.5 yrs of followup) in 5 female patients with lupus nephritis[6]. The patients had an average age of 17 years (range 8–21) at the time of the most recent disease flare. Four of the patients had WHO class IV nephritis and one had WHO class II nephritis. Flare was defined as persistent worsening of the urinary protein excretion and/or other signs of active SLE, such as fever, malar rash, oral/nasal ulceration, Raynaud's phenomenon, and arthritis associated with an increase in the anti-dsDNA and/or a decrease in the serum CH50 value. All patients flared despite treatment with corticosteroids and an immunosuppressive agent[6]. It is important to note that in the above studies, the definition of flare differed from our definition. Currently, there is no uniform definition of flare. Our definition incorporated definitions of flare that have been published in the literature[3,4,7,8]. A recent article by Tseng, *et al* defined flare by the addition of prednisone, cyclophosphamide, azathioprine, mycophenolate mofetil, or methotrexate[8]. After a thorough review of the literature, we felt this definition of flare, as determined by medication change, was the most appropriate for the purposes of our study, particularly as we did not have PGA scores from all visits to allow us to use this tool as a measure of disease flare.

Table 4. Mean pre-flare, flare, and post-flare SLEDAI scores (n = 47)*.

Visit	Mean (SD)	Median	Range
Pre-flare	6.3 (3.5)	5.0	0–16
Flare	7.9 (5.1)	6.0	2–24
Post-flare	5.3 (3.4)	4.0	0–16

* First 5 flare sequences.

Our flare rate was significantly lower than the flare rate for adults with lupus reported by Petri, *et al* of 0.65 flares per patient-year of followup (p < 0.01)[2]. In Petri, *et al*, a flare was defined as an increase ≥ 1 on the PGA compared with the previous visit or a visit within the last 93 days. One hundred eighty-five patients (91% female, 58% African American, 42% Caucasian) with an average age of 35.7 ± 12.0 years were followed prospectively[2]. Compared to the adult cohort, our patients had a slightly higher mean number of flares per patient (1.8 vs 1.5), but had a longer median time to first flare (14.3 vs 12 mo)[2]. Our lower flare rate may be attributed to children having less severe disease, or to treatment being more effective in comparison to adults with lupus.

The average change in the SELENA SLEDAI score of approximately 2 points with disease flare differs from Merino, *et al*, who found an increase of 10.0 ± 5.0 points with a flare in 11 patients with pSLE[5]. The seemingly small change of 2 points with active disease is of importance as it has been shown that the SLEDAI is sensitive to small, but clinically relevant change in lupus disease activity[2,13]. Two-point differences could conceivably be accounted for by mucocutaneous manifestations, serositis (pleurisy and pericarditis), abnormal serologies (low complement and increased DNA binding), or a combination of hematologic (thrombocytopenia and leukopenia) and constitutional (fever) manifestations, which are scored lower on the SLEDAI.

We investigated whether ethnicity may have influenced these results, as non-Caucasian ethnicity in pSLE is a risk factor for a higher incidence of morbidity and mortality compared to Caucasians[14-16]. Indeed, non-Caucasian patients in our cohort did have a significantly higher flare rate than Caucasians (0.58 vs 0.34; p < 0.01).

As with any retrospective study, missing data from patients' records may have influenced our results. We tried to minimize bias by having eligible patients fulfill 4 of 11 criteria for classification of SLE, using stringent criteria for study entry, and having only 1 pediatric rheumatologist perform chart abstractions and calculate the SELENA SLEDAI score.

This is the first large study in pSLE to quantify a change in SELENA SLEDAI score with disease flare. The question remains whether the change in SELENA SLEDAI score is predictive of a flare. Further prospective studies involving a

larger patient cohort will be needed to accurately assess this concern. These studies will only provide useful data, however, if there is a quantitative, uniform definition of flare for pSLE.

Our study of 62 patients with pSLE followed in one institution for over 12 months is the first to report a flare rate of 0.46 flares per patient-year of followup, similar to other reported flare rates in pSLE. The average SLEDAI score preflare was 6.3 ± 3.5. There was a rise of approximately 2 points during a disease flare. Rheumatologists need to be aware of the flare rate in pSLE and that small rises in SLEDAI scores may be clinically significant.

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